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URINARY HYPERACIDITY AND ITS RELATION TO NEURITIS, NEURALGIA AND MYALGIA.

By Thomas R. Brown, M. D.,

Associate in Medicine, Johns Hopkins University.

The etiology of neuritis, neuralgia and myalgia has always been difficult to determine, although we recognize in certain types of cases various causative factors. Thus, for example, in neuritis the only assignable origin in a certain proportion of cases is some poison, introduced into the body from without, or produced within, either due to the action of microorganisms or to defective metabolism. We cannot fail to recognize that many poisons, very different in nature and chemical constitution, show a peculiar tendency to affect the peripheral nerves. In some of these cases other symptoms of poisoning or autointoxication are present, but in a group of cases the only symptoms seem to be the effect of these toxins upon the peripheral nerves. Among the etiological factors may be mentioned metallic poisons, as lead and arsenic, carbon monoxide, alcohol, various drugs, as aniline compounds and sulphonal, and the ptomaines and leucomaines; the toxins produced by fevers, as scarlet fever, diphtheria, typhoid fever, and other infections and poisons in various diseases especially affecting metabolism, as diabetes; affections associated with cachexia, malnutrition and anæmia, where in all probability the resistance of the nerve is lowered, and cold.

When we consider the etiology of neuralgia and myalgia we find very similar factors—various toxins, exogenous or endogenous, conditions of malnutrition and anæmia, cold, organic diseases of the nervous system, some systemic diseases, especially those of the circulatory apparatus, and direct trauma of the nerves or muscles. We must not forget that certain cases, considered as neuralgia or myalgia, are probably in reality mild case of neuritis. There is unquestionably a distinct hereditary predisposition in a certain proportion of all these cases. Certainly in myalgia, and possibly in neuralgia, the feeling is that in a certain number of cases there seems to be a peculiar susceptibility in members of rheumatic or gouty families.

It is not our purpose to discuss the etiology of neuritis, neuralgia and myalgia *in toto,* but simply to call attention to certain interesting features especially in regard to the chemistry of the urine in that group which from lack of definite causative factors can be spoken of as idiopathic. In this discussion while we recognize that these conditions shade imperceptibly into each other; how, for example, many regard neuralgia as a mild neuritis, and others regard myalgia either as a neuritis or a neuralgia, we shall use the terms in the ordinarily accepted sense, and define neuritis as a definite inflammation of the nerve *with* demonstrable signs of inflammation; neuralgia as a pain strictly confined to a nerve or group of

nerves *without* demonstrable signs of inflammation; and myalgia as more diffuse pain affecting certain muscles, or groups of muscles, probably due to changes in their fibrous constituents.

We wish to present a group of cases of neuritis, neuralgia and myalgia, in which the examination of the urine showed a marked increase of acid; to suggest that this is probably due to disturbances of metabolism, and that the pain represents a symptom of autointoxication; and to note that in certain of these cases the administration of alkalies with the consequent diminution of the acidity is associated with marked improvement in the symptoms.

While the acidity of the urine varies within quite considerable limits in health, broadly speaking we may say that when expressed in terms of deci-normal sodium hydroxide solution it is 25, that is, it takes 25 cc. of deci-normal sodium hydroxide solution to neutralize 100 cc. of urine, phenolphthalein being used as the indicator. A number of years ago we made between 100 and 125 observations on normal human beings, and arrived at these figures, which subsequently have been confirmed by other investigators in this field (Hastings); in certain of the text-books of clinical diagnosis (Wood) as well, .25 is given as the average urinary acidity. Of course, this is markedly dependent upon the specific gravity of the urine, which, in turn, is influenced by the exercise taken, and the amount and character of the ingesta; it is lower, often markedly so, when the specific gravity is diminished, as after the ingestion of large amounts of water, and is higher when the specific gravity is increased by the ingestion of too little water, or by an augmented loss of water from the skin or bowels; but under normal conditions, the patient passing about 1500 cc. daily with an average specific gravity of 1.015, the usual acidity is 25 or thereabouts.

In making our observations we examined, as a rule, the early morning specimens, as these probably represent more closely the average urine of the 24 hours than specimens obtained at any other time of the day, and also because, by this means, we can more easily make our examinations shortly after the urine has been voided.

Consideration of Cases.

The series we wish to report comprises 44 cases classified as follows: 5 cases of neuritis, 2 of sciatica, 8 of neuralgia, 11 of neuralgic headache, 5 of lumbago, 1 of torticollis, 23 of myalgia. There were 14 males and 30 females. The youngest case was 16, the oldest 55; no decade predominated.

As regards hereditary predisposition four gave a family history of gout, one of tuberculosis, one of diabetes, one of rheumatism, one of arterio-sclerosis and cerebral hæmorrhage, and one of myalgia and neuralgia. Two of the cases (17 and 19) were sisters, while one (28) was the daughter of two others (16 and 35). It would seem from a consideration of these figures that heredity played a very minor rôle in these conditions.

The digestion and the general habits were good in the great majority of cases; 10 complained of indigestion, either gastric or intestinal, and 10 of constipation, while three used tobacco extensively, six alcohol in considerable amount and five admitted being careless and rapid eaters.

Whether the conditions may be regarded as an expression of a gouty or lithæmic tendency or diathesis is uncertain as six only of the 44 cases could be considered clinically in this category (11, 14, 20, 26, 39, 44).

The hæmoglobin was above 85 per cent in all the cases in which it was taken—a great majority of the 44—with the exception of three (31, 34, 40), in which it was 60, 74 and 70 per cent, respectively. All cases with facial neuralgia or neuralgic headache were especially questioned regarding the condition of their eyes. If there was any suggestion of visual disturbance an oculist was consulted, but in almost all these cases, in fact, with only one or two exceptions, that possibility had already been considered by the patient, and the proper glasses obtained without relieving the symptoms. In the case of the women the suffering was often increased at the menstrual period, at which time, of course, metabolic disturbances are likely to be increased, while in two of the cases the disease came on at the menopause.

It would seem, therefore, that the great majority of these cases developed neuritis, neuralgia and myalgia, not as a result of hereditary predisposition, or indiscretions in diet, exposure to cold or trauma, but from some indefinite cause, as far as we could determine. It, therefore, seems justifiable to regard these cases as idiopathic in origin, and due to a disturbance in metabolism, probably to some circulating toxin, manifesting itself clinically in the production of pain in the affected group of nerves or muscles, associated with an increase in the urinary acidity.

The Urinary Acidity in these Cases.

The acidity was quantitatively determined in each examination, as previously described, from fresh morning specimens. In this series 43 of the 44 cases gave readings, ranging from 35 to 138, and of these 36 had an acidity of 50 or above, 16 of 75 or above, six of over 100, and two of over 125. The average acidity of these 44 cases, which with recurrences furnished 52 readings, was 69.1, that is, nearly three times the normal, 25, as expressed in terms of deci-normal sodium hydroxide solution.

The inspection of our table of cases, however, will demonstrate that the majority show an increase of the specific gravity, and, therefore, it will be fairer to reduce them to a basis of a specific gravity of 1.015, in other words, to determine the acidity if the urine voided were of sufficient dilution to be of the normal degree of density. In 34 of the 44 cases the specific gravity was taken, and the correction made; that is, bringing them to a specific gravity of 1.015 gave an average acidity of 51.5, which shows that although the tendency is to have a urine of higher specific gravity, there is, nevertheless, a real and considerable increase in the acid, the average being a little more than double the normal. In this connection we have assumed that the total amount of solids excreted is the same as under normal conditions, or, in other

REPORT OF CASES.

No.	Diagnosis.	Urinary Acidity and Specific Gravity.	Urinary Acidity Corrected to Sp. Gr. of 1.015.	P. H. = Past History. F. H. = Family History.
1.	Neuritis: r. brachial and circumflex, severe type, followed by disuse and atrophy	115	....	P. H.—Neuralgia and sciatica several years ago—severe one year ago. (Urinary acidity = 60).
2.	Neuritis: r. brachial	50—1.020	37.5	F. H.—Gout (maternal side)
	Recurrence in 7 months	69—1.017	60.9	P. H.—Hard worker, light eater, smokes and drinks in moderation.
3.	Neuritis: l. brachial	69—1.017	60.9	P. H.—Very small eater.
4.	Neuritis: severe r. brachial, ulnar, and circumflex	75—1.015	75	P. H.—Considerable exposure to cold.
5.	Neuritis: severe r. brachial	59—1.022	40.0	P. H.—Much worry. Obesity.
6.	Myalgia: thigh. Neuralgia: leg	61—1.017	53.8	F. H.—Father died of tuberculosis. P. H.—Very small eater, very nervous.
7.	Neuralgia: facial. Myalgia: back	49—1.018	40.8	F. H.—Nervous.
	Recurrence in 4 months	46—1.016	43.1	P. H.—Eczema, attacks of purpura hæmorrhagica.
8.	Neuralgia: arms	51—1.015	51	F. H.—Mother had gout. P. H.—Always nervous, careless eater, drinks considerably at times.
9.	Myalgia: diffuse	51—1.009	85	
10.	Myalgia: shoulder and back	50	....	
11.	Neuralgia: facial. Myalgia	65	....	P. H.—Very neurotic. Constipated.
	Recurrence in 6 weeks	51	....	
12.	Sciatica: left. Lumbago	135	....	Very nervous. Pain in lower back for years.
13.	Myalgia: diffuse. Neuralgic headache	98—1.025	58.8	
14.	Myalgia: diffuse	54	....	P. H.—Alcohol and tobacco in large amounts. Large eater. Constipated. Hard worker.
15.	Lumbago	57—1.015	57	P. H.—Constipated. Gout. Nervous strain.
16.	Myalgia and neuralgic headache	91—1.026	52.5	F. H.—Father had gout. P. H.—Hard worker, careless eater. Has had attacks of epigastric pain and nausea.
17.	Neuralgic headache: severe myalgia of back	68	....	F. H.—Arterio-sclerosis. P. H.—Careless eater, alcohol in considerable amounts. Constipated. Nervous.
18.	Myalgia: diffuse.	49	....	Has epilepsy.
19.	Lumbago	49—1.018	40.8	Menopausal nervousness.
20.	Myalgia: severe, diffuse	88	....	F. H.—Father has diabetes.
	Return of symptoms one year later	101—1.028	54.1	P. H.—Scarlet fever twice. Large, rapid eater.
21.	Neuralgic headache. Myalgia: diffuse	138—1.027	76.6	P. H.—Scarlet fever once. Constipated. Considerable indigestion. Neurasthenia and psychasthenia.
22.	Myalgia: diffuse	85—1.025	51	P. H.—Neurasthenia.
23.	Myalgia: back and legs	55—1.018	45.8	P. H.—Chronic intestinal indigestion.
24.	Myalgia: severe, diffuse	75—1.028	40.2	P. H.—Nervous indigestion. Constipation.
25.	Myalgia	79—1.029	40.9	P. H.—Occasional attacks of acute epigastric pain.
26.	Myalgia: severe, diffuse	99—1.027	55	P. H.—Menopausal nervousness. Obesity.
27.	Torticollis	70	....	P. H.—Tonsillitis as a child. Malaria one year before. Considerable nervous strain.
28.	Sciatica	66—1.018	55	F. H.—Father, Case 16. Mother, Case 35.
	Recurrence in 2 months	55—1.017	48.5	
29.	Myalgia: severe, diffuse	75	....	F. H.—Gout on both sides.
	Recurrence in 8 months	105—1.028	56.3	P. H.—Double ovariotomy 2 years ago. Has distinct beginning gouty deposits in fingers.
	Recurrence in 3 months	75	....	
	Recurrence in 2 months	74	....	
30.	Neuralgic headache	13—1.012	16.3	F. H.—Mother had rheumatism. P. H.—Neurasthenia and nervous dyspepsia.
31.	Myalgia. Neuralgic headaches	78—1.026	45	P. H.—Splanchnoptosis. Hæmoglobin 60%. Indigestion.
32.	Neuralgia: face and arms	80—1.030	40	P. H.—Repeated attacks of tonsillitis.
33.	Myalgia: diffuse	35—1.005	105	
34.	Neuralgic headaches: severe for many years	49—1.015	49	P. H.—Indigestion (hyperchlorhydric). Constipation. Hæmoglobin 74%.
35.	Myalgia: diffuse	52—1.021	37.1	P. H.—Constipation. Nervousness.
36.	Neuralgic headaches. Lumbago	60	....	P. H.—Nervous. Constipated. Hard brain worker.
37.	Neuralgia: facial	60	....	
38.	Neuralgic headaches	70—1.019	55.3	P. H.—Very hard worker, physically and mentally. Splanchnoptosis.
39.	Myalgia	73	....	P. H.—Eats carelessly. Drinks moderately. Hypertrophied heart, and anginoid attacks.
40.	Neuralgia: facial, severe repeated attacks of. Headaches	105	....	P. H.—Constipation. Hæmoglobin 65%.
41.	Attacks of neuralgic headache, followed by digestive disturbances	51—1.024	30.5	P. H.—Digestion poor. Used tobacco immoderately, and alcohol moderately.
42.	Neuralgia: facial	45—1.018	37.5	P. H.—Constipated. Some indigestion. Previously operated on for appendicitis.
43.	Lumbago	48—1.014	51.4	P. H.—Neurasthenia. Pruritus.
44.	Myalgia	75	....	P. H.—Eczema and pruritus.

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words, that the quantity varies inversely with the specific gravity, but more than likely this is not the case, as the solids are probably increased in this group of cases, and, therefore, the total acidity is doubtless higher than the figure given, 51.5.

Increased acidity of the urine is met with in other conditions, and we have described 20 or more cases (Philadelphia Medical Journal, March 2, 1901, New York Medical Journal, March 14, 1903) where the effect of this was to produce symptoms very suggestive of cystitis, notably pain in the bladder and on urination, conditions entirely absent in the present group of cases.

Just why in some instances the brachial nerve, in others certain muscles, and in still others the nerves of the bladder should be selected by the circulating poison or toxin as the source of the signs and symptoms of the individual case we find it impossible to say, but in all probability there have been certain causes in the past history of the patient, which have lowered the resistance of that portion of the body affected.

The Relation of Urinary to Gastric Acidity.

The question may well be asked what is the cause of this increase in the urinary acidity; and does it bear any relation to the acidity of the gastric juice, or is it due to errors in metabolism arising elsewhere? In our series of 44 cases we took test meals in nine, comparing the analysis of the test meal with the specimen of urine obtained at the same time. A study of these cases would seem to show that there is no definite relationship here between the urinary and gastric acidity.

Case	Urinary Acidity.	Corrected to sp. gr. 1.015	Test Meal Free HCl—Total Acid
16	91—1.026	52.5	59—75
19	49—1.018	40.8	0—..
21	138—1.027	76.6	35—50
24	75—1.028	40.2	20—52
25	79—1.029	40.9	43—76
32	80—1.030	40.0	0—22
34	49—1.015	49.0	52—72
41	51—1.024	31.9	0—15
42	45—1.018	37.5	39—63

In nine instances the urinary acidity varied from 45 to 138 or (corrected to a specific gravity of 1.015) from 31.9 to 76.6; the free HCl from 0 to 59, the total acid from 15 to 76, these figures also being expressed in terms of deci-normal sodium hydroxide solution. Of these nine, three had no free HCl; in three the free HCl was between 20 and 40; and in three between 40 and 60. While these are, of course, far too few in number to furnish definite and final conclusions, nevertheless, they suggest that there is little or no relationship between urinary and gastric acidity. It, therefore, seems probable that the urinary hyperacidity met with in these cases is due to metabolic disturbances arising elsewhere, possibly to derangement in the functions of certain of the ferments in the liver or intestines.

It is, of course, quite possible that these cases simply represent a form of atypical gouty manifestation, or a lithæmic tendency. It is worth remembering that in gout and diabetes, with their deranged metabolism, where neuritis and neuralgia are frequent, there is a distinct tendency towards increased acid production, or acid elimination. This naturally suggests that any condition which has as its especial characteristic an increase in the amount of acid produced would seem to possess a peculiar tendency to show symptoms in the nervous tissues, which in turn seem to be peculiarly vulnerable to acids, whatever their chemistry or source of origin.

Treatment.

The treatment of these cases was extremely suggestive along certain lines. In all the cases, believing we were dealing with disturbances of metabolism and that as a consequence toxins were being formed, which in their circulation produced definite lesions or disturbances in certain nerves or muscles, we insisted upon a simple dietary and the drinking of water in considerable amounts; and basing our treatment purely on the urinary findings, we administered alkalies to all in sufficient amount to reduce the urinary acidity to or below normal. It might be well to mention in this connection that in some patients enormous quantities were necessary to bring about this result; thus in a case of very stubborn sciatica of many years' duration, the administration of one ounce of alkali daily for four weeks reduced the acidity of the urine from 138 to only 89, while in many it was necessary to give from half an ounce to an ounce of alkali daily for two or three weeks before the acidity reached normal.

The alkalies given were usually bicarbonate or citrate of soda, carbonate of lithium, and bicarbonate of potash, while if constipation were present calcined magnesia was frequently added.

In some instances the administration of sufficient alkali with the simple dietary and the drinking of large amounts of water was the entire treatment; and in 17 of the 44 cases (1, 2, 3, 7, 9, 10, 14, 16, 22, 24, 25, 26, 28, 31, 34, 37, 39) the cure was effected by this means with little or no additional treatment, but in some other cases it was found necessary to use different therapeutic agents, such as aspirin, coal-tar derivatives, the salicylates, or even opiates occasionally, the paquelin cautery, and the application of heat or cold.

It seems worth while to mention a few of the cases in detail. Three of the five cases of neuritis obtained almost entire relief in a comparatively short time under this treatment, and one of these (1) had previously been obliged, for between three and four weeks, to take from $\frac{1}{2}$ to 1 grain of morphia daily; the other two cases of neuritis, however, needed sedatives of some kind. One patient (7) with neuralgia and myalgia had noted before he came that his attacks could be stopped by taking large quantities of bicarbonate of soda, while in several of the milder cases (9, 10, 14, 15, etc.) almost complete relief was obtained in a few days' time. In some (14, 20, etc.) it seemed that the regulation of the diet, and the general regimen was really of much greater importance than the administration of alkalies.

That there was an inherent tendency towards this condition was shown by the fact that a number showed a recurrence of

symptoms if the regimen was stopped, though in others it seemed to produce entire relief for long periods of time.

It was possible sometimes to examine the urine after the patient had been under treatment for a certain length of time, and it is interesting to note the decrease in acidity that we obtained. Of 16, whose urine was examined after they were either cured or greatly improved, the average acidity was 21.5, but if the acidity was corrected to a specific gravity of 1.015 the acidity was 24, that is practically normal; the closeness of these figures would suggest that the improvement was not so much due to the dilution of the urine as to the reduction of its acid.

In all suffering from anæmia, iron sometimes combined with arsenic, was given (31, 34, 40) while in one case (41) alkalies had no effect on the pain, but the administration of free HCl to correct the functional anacidity of the stomach was productive of almost immediate beneficial results, and this would suggest that in probably a small proportion of cases the fundamental trouble is the disturbance of gastric secretion.

This study seems to show that the benefit of the thorough alkalinization of the patient in these conditions was often sufficiently striking to warrant its trial.

Whether this beneficial effect shows that the toxins produced are really acid in nature, and are, therefore, neutralized and rendered less harmful by neutralization with alkalies, or whether the effect of increased water drinking, simple diet and alkalies is mainly to improve digestion and stimulate elimination we cannot say, although the former view is certainly suggested by the very rapid and marked improvement met with by the administration of alkalies in a certain proportion of these cases, in some, in fact, to such an extent that it almost suggests an elective action.

CONCLUSIONS.

In this article, very brief and fragmentary as it is, we have shown that in a certain group of cases of neuritis, neuralgia and myalgia, which for want of a better term, and in the absence of definite or sufficient etiological factors may be called idiopathic, there is a definite increase in the acid eliminated, although we have not attempted to determine whether this is due to an increase in the acid phosphates, or in the organic acids. We believe, however, that the latter is more likely, and we hope subsequently to investigate this phase of the subject in detail. For want of a better explanation we make the suggestion that this hyperacidity is probably the urinary expression of some abnormality or error of metabolism, probably having little or no relationship with the gastric digestion or the degree of acid in the gastric contents, but more probably due to metabolic disturbances arising lower down in the digestive tract; and that the pain and other manifestations in the nerves or muscles affected are due to some circulating poison or toxin, the condition thus probably being a form of endogenous intoxication. Why certain groups of nerves or muscles should be selected in some cases, other groups in other cases, we are unable to say, though in all probability there has been something in the past history of the patient as trauma, exposure to cold, etc., which has lowered the resistance of the especial nerve or muscle affected.

Finally it seems certain that in some patients the insistence upon a simple dietary and copious water drinking, and, most important of all, the administration of alkalies in sufficient amount to reduce the acidity of the urine to normal, is followed by a very marked amelioration of symptoms; and in a few by their complete disappearance without the aid of other remedial agents.

AN ANALYSIS OF THE COURSE OF LABOR IN 100 OCCIPUT POSTERIOR PRESENTATIONS.

By CLARENCE B. INGRAHAM, M. D., Denver, Colorado.

In view of the fact that when the occiput occupies a posterior position in the pelvis the condition is commonly supposed to cause considerable difficulty to the progress of labor, and to be of more or less serious consequence to both mother and child, I have collected one hundred consecutive cases, occurring in the obstetrical department of the Johns Hopkins Hospital, in order to show that this variety is to be regarded with but little more anxiety than the more common occiput anterior presentation.

Though the figures of the different observers vary quite markedly, occiput posterior presentations are of frequent occurrence. Pinard and Dubois having found them in 49.8 and 26.23 per cent of their cases; while in this clinic, in a series of cases studied by Dr. Williams, there were 16.8 per cent. This smaller number he attributes to the fact that the examinations were made late in labor when anterior rotation had already occurred. In my series the percentage is still smaller, 12.03 per cent, due probably to the fact that where the least doubt has existed as to the variety of position, the cases have been discarded, and several diagnosed as of transverse variety really belonged in this number.

All the babies in this series were born at term, and those cases with small children were discarded as not being fair examples for comparison in difficult labor. To be sure of the position of the child, in practically every instance, an internal as well as an external examination was made and the variety of position verified.

In looking for a cause of the occurrence of this variety of position, it was found, in this small series at least, that the condition was slightly more common in the contracted pelvis—the number occurring in normal pelves was 85, while in 15 the pelvis was contracted as follows: Generally contracted in

nine, simply flat in two, generally contracted rachitic in one, and funnel pelvis in two cases. The percentage of contracted pelves occurring in the hospital being 13.1 per cent, makes an increase of 1.9 per cent in association with the occiput posterior presentation. Forty-eight of the 100 cases were in multiparæ and 42 in primiparæ. Taking into consideration the cephalic measurements, nothing of importance was gained, the average measurements obtained from the 100 heads being:

	Cm.
Fronto-occipital	11.73
Biparietal	9.38
Bitemporal	7.90
Mento-occipital	13.92
Suboccipito-bregmatic	9.59
Suboccipito-bregmatic circumference	31.80

All of which are seen to be practically normal.

Up to this time, the percentage of operative deliveries at term in the Johns Hopkins Hospital, including posterior positions, is 15.2 per cent, which, though high, is due to the fact that many patients are brought in from outside only because complications have arisen. The number of cases requiring operation in the 100 posterior positions was 18, but slightly higher (2.6 per cent) than that of all cases, and of these 18, 11 were due to causes known to be from conditions other than the posterior position, for example:

	Cases.
Mitral stenosis (patients not allowed to continue in second stage of labor)	2
Contracted pelves	4
Prolapsus of cord	1
Eclampsia	1
Dead infected fœtus	1
Ventral hernia and relaxed abdominal muscles	1
Ankylosis of coccyx	1

Of the remaining seven operative cases, the indications given are as follows:

1—Mid-forceps—R. O. T.—P. Poor pains, in second stage 2 hours and 53 minutes with no advance.

2—Mid-forceps—R. O. P. Fœtal and maternal pulse the indication.

3—Mid-forceps—L. O. T.—P. In second stage 2 hours and 10 minutes. Appearance of mecomium and increased rate of fœtal heart.

4—Mid-forceps.—R. O. T.—P. Relaxed abdominal wall and insufficient vis-a-tergo. Second stage 2 hours and 45 minutes.

5—Mid-forceps—R. O. T.—P. In second stage 3 hours with no advance. Maternal pulse 110 to the minute. Exhaustion.

6—Low-forceps—R. O. P. (Scanzoni application). In second stage for over 2 hours with no advance.

7—Attempted high-forceps—R. O. P. Maternal pulse 130 to the minute. In second stage 3 hours with no advance. Version and extraction. In this case the dystocia seemed to be due almost entirely to the very large size of the child, which was 57 cm. long and weighed 4110 gm. The head measurements were:

	Cm.
O. M.	14.50
O. F.	11.00
Bi-P.	9.50
Bi-T.	8.00
S. O. B.	10.00
S. O. B. circum.	32.50

In case four it is doubtful if the variety of position was a factor.

Among these 100 cases, there were seven in which the occiput rotated into the hollow of the sacrum—a condition in which operative interference is quite generally supposed to be necessary; but of these seven, one only required operation, a delivery with low forceps. The remaining six were born readily and spontaneously, the second stage of labor averaging but one hour and two minutes.

In considering the duration of labor for the primiparæ in whom spontaneous anterior rotation occurred, the average was found to be 18 hours and six minutes—the first stage averaging 16 hours and 10 minutes, and the second stage one hour and 42 minutes. For the multiparæ, the average duration was 10 hours and 15 minutes, of which the first stage occupied nine hours and ten minutes, and the second stage 52 minutes.

In the cases in which rotation occurred into the hollow of the sacrum, the labors averaged 14 hours and seven minutes, of which the first stage was 13 hours and the second stage one hour and two minutes. It might be supposed that this condition would require a much longer time, but of these seven cases, five were multiparæ; and unfortunately, with the two cases of primiparæ the time cannot be determined as in one case forceps were applied at the end of two hours, and in the other, the first and second stages were not estimated separately, and both together lasted 10 hours and a half. Also three of the babies were under 3000 grams in weight, the only ones in the series below this figure.

When one compares the duration of labor in this series with that of the various text-books, we find that Williams estimates the first stage as 16 hours, and the second one hour and three-quarters to two hours for primiparæ; and for multiparæ, 12 hours and one hour, respectively. Veit gives the duration of labor as 20 hours for primiparæ, and 12 hours for multiparæ. Varnier, from the records of 2000 cases, one-half of which were primiparæ, estimates it as $13\frac{1}{2}$ and $7\frac{1}{2}$ hours, respectively—the second stage 75 minutes in the former and 35 minutes in the latter. It is seen that, as compared to the times of the first two observers, with this series of occiput posterior presentations the duration is short, while with Varnier's figures it is somewhat longer.

The percentage of perineal tears received during these 100 cases was 26 per cent as against 23 per cent in 200 consecutive cases of the more common anterior variety. Of these 26 perineal tears, 18 were in primiparæ, and eight in multiparæ; 14 of the first and 12 of the second degree. Twelve of the tears were in operative cases, and of these, four were of the first and the remaining eight of the second degree.

Of the seven cases in which the occiput rotated posteriorly there were four tears (55 per cent). This is readily explained when we consider that the vulva, with the more unusual mechanism of labor, is stretched to admit the occipito-frontal diameter of the head (11.75 cm.) instead of the suboccipito-bregmatic diameter (9.5 cm.) in the occiput anterior variety. In the three remaining cases, in which the occiput

rotated posteriorly and there were no perineal tears, the babies were under 3000 grams in weight.

Of the 100 cases there were five fœtal deaths. One baby lived six days with congenital deformity of the viscera and broncho-pneumonia; one had congenital absence of the pylorus and lived a few days; one with status lymphaticus lived 1½ hours after version and extraction; one was practically still-born; with this child, version and extraction was tried through a funnel pelvis and abandoned for a second attempt with the forceps, by which the head was unduly compressed; and one child died through perforation of the head; there was a generally contracted pelvis and a long labor without engagement of the head. Aecouchement forcé was done, and an attempt with forceps on the floating head tried, which was unsuccessful. Version and extraction was then resorted to. The head became wedged in the pelvis and perforation of the after coming head beeame necessary. The conjugata vera measured 10.5 cm., and in this ease the method of procedure should have been pubiotomy. Of these deaths, the last two were due to operations dependent upon eontracted pelves; in one the pelvis was generally contracted, and in the other funnel shaped. The posterior variety of position cannot be held responsible for either one.

Three other babies were slightly asphyxiated at birth. In one there was a pressure necrosis of the sealp from a contracted pelvis, and in another a facial paralysis followed the application of forceps. Both recovered completely.

In the series there were two maternal deaths—one patient died of typhoid fever during the puerperium, the disease being present at the time of labor; the other lived one day after delivery, and died from chronic myocarditis with dilatation.

In reviewing this rather small series of oeciput posterior presentations, it is shown that operative interference need be but little more frequent than in the occiput anterior variety of presentation. The duration of labor is slightly more prolonged and the percentage of perineal tears slightly higher than in the anterior variety. The consequences to the mother and child are, however, not mueh more serious.

It is the procedure in this clinic, when a posterior variety of position is diagnosed, to leave the condition to nature, when, as is shown in almost the same percentage of cases as in occiput anterior the labor is spontaneous. Many writers advocate turning the head to an anterior variety by means of the hand introdueed into the vagina. This proeedure renders the patient more liable to infection through manipulation; and while in a eertain number of cases, if sueeessful, it may hasten the labor, in the majority, rotation to the symphysis takes place spontaneously (about 92 per cent), and the labor is uncomplicated.

To quote Dr. Williams from his text-book:

"Even when the occiput rotates into the hollow of the sacrum, the prognosis is not so very bad, as in the majority of cases spontaneous labor usually occurs. No doubt, when the occiput remains posterior, there is an increased tendency toward perineal tears, which is particularly marked when the head is born by the less frequent mechanism. But to my mind, the main cause of the dread in which posterior presentations are held is the fact that they frequently escape recognition, and accordingly, if for any reason operative delivery becomes necessary, the forceps is applied improperly—that is, as in occipito-anterior presentations.

"When occipito-posterior presentations have descended into the pelvis, it is my practice to leave them to nature so long as possible, and to interfere only when absolutely necessary. But when convinced that the best interests of the mother and child will be subserved by prompt delivery, forceps should be applied.

"On the other hand, when the head is arrested at the superior strait in a posterior position, version should be resorted to as soon as one is convinced that spontaneous advance will not occur, provided of course, that the operation is feasible and is not contraindicated by disproportion between the size of the head and the pelvis."

As regards the application of forceps, when the occiput has rotated into the hollow of the saerum and interferenee becomes necessary, the forceps is applied in the usual manner to the sides of the head with the pelvic eurve toward the face, and the occiput drawn out slowly over the perineum in a horizontal direction until the forehead or root of the nose engages under the symphysis, after which the oceiput should be delivered over the anterior margin of the perineum by slowly elevating the handles. Then, by imparting a downward motion to the instrument, the forehead, nose, and chin sussessively emerge from the vulva.

When interference is indicated in an obliquely posterior variety it is attempted to rotate the head to a transverse or even an anterior variety by means of the hands, and then apply forceps in the usual manner. If, however, this cannot be effected the double application of forceps by Scanzoni's method is resorted to and has given sueh excellent results that it is employed to the exelusion of all other methods.

In the first application, while the oeciput is obliquely posterior, the blades are applied to the sides of the head with the pelvie eurve looking toward the faee of the child, and downward traction is made until the head impinges on the pelvic floor, when a rotary movement is imparted to the forceps, by which the occiput is slowly brought into a transverse or obliquely anterior position. The forceps, which have become inverted, are taken off, and reapplied in the usual manner for the anterior variety—that is, with the pelvic curve toward the oeeiput, which is now rotated so as to lie under the symphysis, when the extraction is completed in the usual way.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

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INVESTIGATION INTO SEVERAL CASES OF POISONING BY VAPORS OF "C. P." BENZOL.

By Charles Glaser, Baltimore.

A little over a year ago I was asked to inspect a can-factory in this city and discover, if possible, the causes which had led to the poisoning of a number of the employees. All of the victims were young girls, and four of them had been removed to the Johns Hopkins Hospital, where one had died, another had been reported dangerously ill, while the remaining two were found in less alarming states.

The attending physician of the hospital joined me in the inspection of the factory, and at the same time examined 14 girls, aged 14 to 18 years, and employed in the same building from which the four victims, first mentioned, had been removed. A number of the men were also examined. All were found to be highly anemic.

The principal work carried on in the building where these people were employed, consisted in preparing the tops of the cans for sealing. Four machines, each one attended by four girls, carried on this operation. The tops, carried by mechanical means, were passed under a brush, and this, also mechanically, provided each disc near its outer edge, with a rim of rubber dissolved in benzol, and thickened by means of bole and ground asbestos.

Two of the girls were employed at this work, whereas the other two spread the tops, after they had passed out of the machine, on racks to dry. Upon evaporation of the benzol there is left a thin rubber ring near the margin of each top, and this makes possible an hermetic closure.

Although all the windows were open, the air in the building, particularly in the vicinity of the machines, smelled strongly of benzol. Upon inquiry it was stated that about 10 gallons of the rubber solution had been used daily for the preceding six months. During this time several large lots had been consumed without detrimental effects of any kind, and it was not until a certain drum marked No. 36 began to be used, that sickness appeared.

A small sample of benzol from drum No. 36 was tested, with the following results:

Specific gravity at $15\frac{1}{2}^\circ$ C. = 0.880.

Sulphuric acid gave a distinct straw-yellow color.

Carbon bisulphide was found present in small quantity by the xanthogenate test.

Anilin and nitrobenzol were shown to be present in traces by Jacquemin's test.

A larger sample of benzol No. 36 was thereupon obtained from the factory, and of this 200 cc. were carefully fractionated with the aid of a Le Bel head.

The initial boiling-point was 80° C. which rose gradually to $85\frac{1}{2}^\circ$ C., when 190 cc. had distilled over. The remaining 10 cc. were tested for aniline with negative results, and for nitrobenzol, which gave a strong dark blue coloration by Jacquemin's test.

The first death (that of patient W.) had occurred a few days before I was called in, and this case was out of reach of a chemical examination. The attending physician, however, submitted samples of urine from two of the other patients. C., who was critically ill, and died soon afterward; N., who was not so seriously ill, and who finally recovered.

The examination of these urines was conducted as follows: they were distilled in a current of steam, the distillates were exhausted with ether, and the aqueous residues discarded.

To the ether 5 cc. of $\frac{n}{10}$ sulphuric acid was added, and after shaking, run off. After this the ether was washed several times with small quantities of water. The united acid liquids were then neutralized with solid sodium carbonate. One drop of phenol, and several drops of a sodium hypochlorite solution were added. Case C. gave a strong blue color reaction for aniline.

The ether from which the sulphuric acid had been abstracted was tested for nitrobenzol with negative results in the following manner: it was allowed to evaporate spontaneously until only a little remained; upon the addition of alcohol the liquid was transferred to a flask with a long reflex tube; sulphuric acid and zinc were now added, and the mixture in the flask left in a warm place, usually over night. After neutralization, the aniline formed was extracted with ether, and treated as before described.

Case N. gave a faint blue color reaction for aniline. The ether in this case gave a distinct, but not clean blue color reaction when tested for nitrobenzol. This effect may have been due to a small remnant of aniline, a trace of nitrobenzol, or to the presence in the urine of some other substance capable of giving imperfectly and deceptively a test more or less blurred for aniline after reduction.

The urine of another patient, who had nothing to do with the benzol cases, was submitted by the attending physician, and gave, after steam distillation, and further identical treatment, a negative test for aniline, but a faint brown reaction turning slowly to a faint dirty green when tested for nitrobenzol.

The two cases, N. and C., seem to show an interesting connection between the severity of the cases and the strength of the reactions obtained for aniline.

After the death of patient C. her brain was submitted for analysis. About one-fourth of its was pulped, acidulated, and subjected to distillation in a current of steam. Four hundred cubic centimeters of distillate were obtained.

The distillate was exhausted with ether and the latter examined as before described. Only a trace-reaction for aniline was obtained, and a very faint apparent reaction for nitrobenzol, which could not be positively identified by a control test for isonitril. For this reason the latter reaction was considered as probably due to the same substance that gave a

similarly indistinct reaction in the urine not connected with the benzol cases.

The residue in the still was now made distinctly alkaline by means of sodium hydroxide, and about 250 cc. were distilled over by steam. The distillate was then extracted with ether, and the ether was treated as stated before.

Jacquemin's test gave a very distinct sky blue color.

As the history of these cases is on file at the Johns Hopkins Hospital, I only wish to point out here, that the symptoms of a slow, chronic poisoning by minute quantities of nitrobenzol, are quite different from those of acute cases,[1] so much so, that the attending physicians at the hospital doubted my results, until, in the presence of one of them, I demonstrated aniline in the two urines which had been submitted, and in the brain of the patient who died.

The conclusions to be drawn from these examinations are positive and direct. The cause of the sickness and deaths was the aniline which had been absorbed during long periods in the shape of nitrobenzol and had accumulated in the body until sufficient to cause trouble.

Benzol itself has been at times declared to be perfectly harmless, and at times has been denounced as dangerous.[2]

In some of the cases on record in the literature [3] it is stated that aniline and nitrobenzol were absent. In view of the fact that nitrobenzol was concerned in the cases under discussion, it appears probable, that its presence in minute quantities may have been overlooked for want of sensitiveness in the methods employed.

A rough attempt was made to get at the magnitude of the amounts of nitrobenzol present in benzol by comparing the intensity of the color produced by Jacquemin's test with pure benzol to which known quantities of nitrobenzol had been added. It appeared from these tests that the quantities of nitrobenzol in the fluids analyzed, fluctuated from 1 to 7 mg. per liter. Assuming 5 mg. as the average, 10 gallons or nearly 38 liters per day of the rubber solution used in the factory would contain 190 mg. of nitrobenzol, a quantity, which, for chronic effects, is certainly not negligible. The quantities of aniline present were much smaller, and in the present connection may be neglected.

During the time that the aforementioned analyses were made, samples of various lots of benzol used by the can company during the preceding six months were also examined. The results are tabulated below.

Sample.	Aniline.	Nitrobenzol.	Remarks.
1.	Extremely faint.	None.	Standard by which contract was made.
2.	Extremely faint.	Extremely faint.	59 days later.
Drum No. 36.	None.	Strong dark blue color.	
Drum No. 37.	Faint light blue color.	Distinct light blue color.	
Drum No. 38.	Extremely faint trace.	Strong dark blue color.	
Drum No. 39.	None.	Distinct light blue.	
Drum No. 40.	Very faint trace.	Very faint trace, barely visible blue tint.	

The gap of about 120 days between sample No. 2 and drum No. 36 is regrettable as it is possible that more definite information as to the cause of the presence of the nitrobenzol might have been obtained. The tests, however, show that commercially C. P. benzol, free from nitrobenzol, can be, and at times was, furnished. That nitrobenzol should have appeared in quantities large enough to cause sickness and death, and should then have disappeared again completely, points to some accidental admixture, possibly by the temporary use of some of the drums for storage of nitrobenzol, followed by insufficient cleaning.

Since "C. P." benzol is used largely in the industries, and consequently a considerable number of people are more or less exposed to its vapors, the can company kindly gave me permission to make public the results of my investigation.

[1] Allen, Commercial Organic Analysis, 3d Ed., Vol. 2, Part 2, p. 168.

[2] Wichern: Fabriksfeuerwehr, 1909, Vol. 16, pp. 10-11, 13-14. Benzinevergiftung, München. med. Wchnschr., 1909, Vol. 56, p. 11.

[3] Santesson: Arch. f. Hygiene, Vol. XXI, 1897.

THE VISCOSITY OF THE BLOOD IN HEALTH AND DISEASE.

By CHARLES R. AUSTRIAN, M. D.,
Medical House Officer, Johns Hopkins Hospital.

(*From the Medical Clinic of the Johns Hopkins Hospital and University.*)

The study of the viscosity of the blood, like the investigation of its other physical properties, was first undertaken with the idea of discovering a further aid to clinical diagnosis and to indicate new therapeutic paths. Many methods for measuring the viscosity have been devised, a critical review of which is given in a recent article by Determann.[1]

The work here reported will be dealt with under two captions:

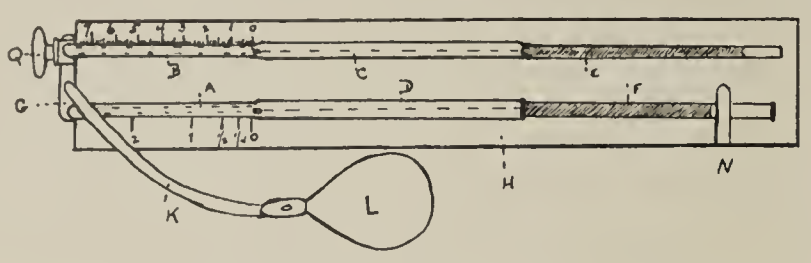
I. The viscosity of the blood in normal individuals, including a consideration of the factors concerned in the production of the viscosity.

II. The viscosity of the blood in disease, a collection of numerous clinical observations in various diseases with an explanation, where possible, of the changes which occur.

In all the determinations made, the Hess [2] Viscosimeter was used. The instrument is not well known in this country so a description of it may not be amiss.

On an opaque glass base, H (see drawing), two graduated glass tubes, A and B, are fastened which are connected at one end by a third tube, G, and this in turn is in communication through a branch with the rubber balloon, L. At the other end, the two tubes, C and D, are drawn to capillaries of very

fine caliber which widen again to the bore of A and B. The tube, F, placed on H and held there by the support N, is removable, and can be replaced by any of a number of similar ones. By means of the stop-cock Q, it is possible to establish or to interrupt the communication between B and G, and so between B and the balloon L. The tubes A and B are bent to a right angle at their junction with G. Interposed between the rubber tube K, and the balloon L, is a glass tube which communicates by an opening with the air.



Hess Viscosimeter.

The entire apparatus is contained in a case 29 x 9 x 6 cm., having compartments for tubes similar to F, for a flask of ammonia, to be used in cleaning the instrument, and a thermometer mounted on H.

The method of making determinations is as follows: In the tube B-C-E is a column of distilled water, the left meniscus of which is at 0 (zero). A tube F is filled by capillary action with blood. It is then placed in position end to end with D, and by means of suction exerted by L the blood column is drawn up to 0 (zero). The cock Q is then opened and under the suction of the bulb, the water and blood flow through the tubes A and B.

As soon as the blood reaches 1 (on the scale) suction is discontinued and the readings are made. The mass of water which has risen in B, as shown on the scale, gives the relation of the viscosity of the blood in question to that of distilled water.

Water and blood are now expelled by pressure on the bulb L, the cock Q being closed when the water reaches 0 (zero). F is removed, and the tube DA is cleaned with ammonia twice drawn into it.

If the blood is very viscid or coagulates rapidly, it may be drawn to one-half or one-fourth, and the values obtained multiplied by 2 or 4, respectively.

Controls made with fluids of known viscosity show an accuracy within 1-2 per cent.

Experiments by Hess showed, that with every rise in temperature of 1° C., the viscosity decreases 0.8 per cent. Observations at ordinary room temperatures show an error of about 4 per cent which, in relation to other errors which may arise due to the personal equation, is negligible. A correction is necessary, then, only when there are great variations in the temperature.

The blood for our experiments was obtained from a needle stab in the ear lobule, previously cleaned with alcohol. In those cases in which determinations on the plasma were made, the blood was drawn from the median basilic vein by venepuncture, and coagulation was retarded by the addition of dry hirudin * as recommended by Determann.[3]

In making the determinations, an absolutely fixed temperature was not maintained, the suction force varied, and errors probably arose in drawing the blood. These factors, however, were present in all the experiments, could not be excluded, and therefore do not vitiate the results.

I. The Viscosity of the Blood in Normal Individuals.

The normal viscosity is difficult to determine; first, because it is not always easy to decide just who is normal; and second, because of marked physiological variations in the viscosity of the blood. That various observers do not agree as to the normal, is shown by the table here given:

			Man.	Woman.
Hess [4]	4.57	Determann [8]	4.798	4.516
Bence [5]	5.4	Kottmann [9]	5.11	
Rotky [6]	5.12	Robert-Tissot [10]	4.79	4.51
Hirsch & Beck [7]	5.1			

We chose for these observations students varying in age from 21 to 28 years—robust young men. The readings showed:

5.0	4.8	4.5	4.4	4.5
4.6	4.6	4.7	4.3	4.5
4.4	4.4	4.4	4.6	4.4
4.7	4.5	4.6	4.5	46
4.5	4.4	4.6	4.7	4.5

The average in these cases gives 4.55 as the viscosity for adult men between the ages of 20 and 30 years.

Similar determinations made on healthy women, in the same decade of life, showed:

4.5	5.0	4.6	4.3	4.5
4.7	4.5	4.3	4.5	4.3
4.9	4.3	4.8	4.6	4.4
4.6	4.5	4.5	4.4	4.2
4.8	4.3	4.3	4.7	4.3

Thus the normal for women—4.51—is very little different from that in men.

Hess [4] and others have shown that the viscosity of the blood varies with age. Low values as 3.89 (male) and 3.80 (female) present in the first decade, are supplanted by rising values as life advances.

Variations with the time of day, digestion, rest in bed, muscular activity, body weight, body temperature, menstruation, pregnancy, etc., have been previously noted.

The relative importance of the other physical and chemical properties of the blood in determining its viscosity, is much mooted. Viscosity does not vary directly with the specific gravity—"low viscosity values occur with high specific gravity

* Hirudin is a scaly solid, soluble in water, obtained from an extract of the buccal glands of the leech—Hirudo medicinalis. It has the power of retarding coagulation of the blood even when used in minute quantities, and has no influence on viscosity.

and conversely, due probably to the fact that, whereas all the elements of the blood enter into the production of the specific gravity, only some of them influence the viscosity" (Adam [11]). For the blood is not iso-viscous, the more viscid substances bound in the erythrocytes losing some of their potency.

That hæmoglobin and viscosity do not always vary in direct proportion is shown below:

Hæmoglobin.	Viscosity.	Hæmoglobin.	Viscosity.
50	3.2	30	3.0
79	4.5	100	5.0
58	4.5	60	3.8
95	4.5	42	2.6
80	4.3	75	4.2
95	4.0	73	3.4

As to the constancy of the relation between the number of the red corpuscles and the viscosity of the blood, no little discussion has arisen. Determann (*l. c.*[8]) notes that "though a fairly close parallel exists between the two, so many exceptions are found, that on the determination of the red-cell count no safe inference as to the viscosity can be drawn." Burton-Opitz,[12] on the other hand, maintains that "the red corpuscles are the principal factor in determining the viscosity of the blood."

In our earlier observations, it seemed that a direct relation between these two factors could be demonstrated. So close indeed did this relation seem, that we felt able to estimate the red-cell count from the readings obtained on the viscosimeter. Subsequent series of observations, however, have shown that though the viscosity of the blood and the number of the erythrocytes frequently do vary in direct proportion, in many instances no close parallelism can be proved.

R. B. C.	Viscosity.	R. B. C.	Viscosity.
4840000	2.9	3120000	3.1
3650000	3.6	4000000	4.3
3900000	3.2	2080000	2.6
4130000	2.6	2100000	2.0
4480000	4.4	4220000	4.1
2200000	2.6	4900000	4.1
4320000	4.4	3700000	4.0
4000000	4.3	3900000	4.0
4100000	3.9	4000000	5.0
3700000	3.9	4000000	4.3
4300000	4.6	3800000	4.2
4700000	4.6	4400000	4.2
5600000	4.7	2760000	3.0
6400000	5.5	3300000	3.0
4200000	4.7	5120000	5.1
5800000	4.9	4700000	5.0
6800000	5.2	5000000	4.5
4200000	4.2	4320000	4.6
3200000	3.4	2975000	3.1
3850000	4.6	4100000	3.3

In order to estimate, if possible, of just how much importance the red corpuscles are in determining the viscosity of the blood, the following experiments were performed:

Twenty cubic centimeters of blood were drawn under aseptic conditions from the median basilic vein, into a syringe containing 2 mgm. of dry hirudin and the viscosity of the whole blood determined. A part of this blood was centrifugalized until sedimentation of the formed elements was complete. The supernatant plasma was pipetted off and the viscosity of it measured. The corpuscles were then washed with physiological saline solution, and suspensions made, until the cell count was the same as that of the blood used. The viscosity of this suspension was then determined, and making allowance for that of the saline solution, we had the coefficient for the red corpuscles.

Blood.	Plasma.	R. B. C.	Saline.
5.2	1.9	2.4	1
4.6	1.7	2.2	..
4.5	1.8	2.0	..
4.7	2.0	2.3	..
4.3	1.8	1.9	..
5.0	1.7	2.2	..
4.9	1.9	2.4	..
4.4	1.9	1.9	..
5.1	2.0	2.6	..

From these findings it seems evident that though the number of red cells in the blood is an important factor, it cannot be the dominant element in determining the viscosity of the blood. The significance of the plasma is also well shown, and variation in its composition must be of no little moment in causing fluctuations in the coefficient for the whole blood.

The influence of hæmoglobin on the viscosity has been demonstrated by Adam (*l. c.*). This author noted that in centrifugating blood, whenever slight hæmolysis occurred, the coefficient of the tinted plasma was higher than when a clear plasma was obtained. In order to prove whether the increased viscosity was due to hæmoglobin, he dissolved crystals of horse hæmoglobin in human plasma and found rising values with increasing concentrations. He then laked blood by alternately freezing and warming it, and found on centrifugation two layers—the upper, a colloidal fluid free of corpuscles with a coefficient higher than that of the whole blood; the lower layer was so thick with the stroma of the cells that its viscosity was extremely great. The increased viscosity of the laked blood is probably due largely to the increased protein content of the plasma, consisting mainly of hæmoglobin. That this last is true, he showed by demonstrating that, whereas carbon dioxide passed into normal plasma had no effect on its coefficient, when it was passed into the plasma of hæmolyzed blood a rise in viscosity occurred.

The observations on the plasma of whole and of laked blood we have been able to confirm in a series of ten cases.

Case.	Normal blood.	Laked blood.	Normal plasma.	Laked blood plasma.
I	4.9	5.7	1.9	5.1
II	4.5	5.2	1.8	4.7
III	4.0	5.9	1.9	4.3
IV	4.6	5.2	1.7	4.8
V	5.0	5.9	2.0	5.1
VI	4.3	5.0	1.8	4.4
VII	4.4	5.1	1.7	4.6
VIII	4.6	5.3	2.0	4.7
IX	4.7	5.4	1.8	4.8
X	4.5	5.6	1.9	4.8

This relation between whole and laked blood had previously been pointed out by Determann (*l. c.*[8]), who explained the higher readings in the hæmolyzed blood as due to the libera-

tion of highly viscid substances, normally contained within the stroma of the erythrocytes, and thus prevented from influencing the viscosity of the whole blood. He found clinical evidence to support this view in observations on a case of black water fever with hæmoglobinæmia, in which, while the patient was well, the laked and the whole blood differed greatly in viscosity, whereas during an attack of hæmoglobinuria the difference was less marked. In this instance, too, he had an indication that the viscosity of the blood is to some extent at least dependent on the osmotic tension between the plasma and the red corpuscles, and the difference between the coefficients of whole and of laked blood may perhaps be an expression of the resistance or fragility of the red corpuscles in health and in disease.

A priori, the proteid content of the blood would be an important element in the production of the viscosity of the blood, and support is given this hypothesis by the experiments of Burton-Opitz [13] on animals and by the observations of Determann (*l. c.*[8]) on man.

The former noted that the blood of dogs fed on meat has a higher viscosity than that of dogs, hungry, or on a low proteid diet. He also found that food rich in fat raises the coefficient of the serum especially, whereas proteid food raises that of the whole blood.

Determann (*l. c.*[8]), studying the viscosity in vegetarians and in meat eaters, found that the coefficient in the former was low compared to that of the latter—4.32 : 4.85, though the hæmoglobin, specific gravity, and the number of the formed elements of the blood were not different. If these findings stand the test of further observations, they may furnish a valuable clue to dietetic regulation in those diseases in which it seems advisable to reduce the viscosity of the blood. The metabolic experiments of Bence (*l. c.*), however, showed no changes in the viscosity of the blood after the use of diets over short periods of time. Similarly, in 35 cases of cardiac disease in the Johns Hopkins Hospital, the feeding of a modified Oertel diet, over periods of from two to six weeks caused no appreciable alteration in the viscosity coefficients.

The influence of various salts has also been studied by Adam (*l. c.*). In a series of careful experiments, this author found that the viscosity of a solution rises with the increase of its proteid content and in general with the salt concentration. "But all salts do not influence viscosity to the same degree, the multivalent salts having a greater influence than the univalent. Among the latter, the iodides and potassium bromide are unique, in that they decrease the viscosity." This last observation lends support to the work of Müller and Inada [14] that iodides, given therapeutically, diminish the viscosity of the blood, but Adam asserts "that ordinary doses of the iodides rarely have a viscosity-lowering action, and at times even a viscosity-raising effect may be noted."

That the gaseous content of the blood is important in its effect on viscosity, has long been recognized. Koryani and Bence [15] found maximal values when saturation of the blood with carbon dioxide was reached, and that as this gas was replaced by oxygen, the viscosity decreased to a minimum beyond which the further addition of oxygen caused it to rise again. The work of Hamburger [16] and of Limbeck [17] indicated that as the carbonic acid content of the blood increases, the red corpuscles take up water and anions from the plasma, whereby the volume of each cell becomes greater, while the proteid, fat and sugar content, the mass of dry residue, specific gravity and osmotic pressure of the plasma rise, to fall again when the carbon dioxide is driven out.

Burton-Opitz [18] demonstrated similar changes by having dogs breathe alternately normal air and air surcharged with carbon dioxide, and Rotky (*l. c.*) noted a decrease in the viscosity of the blood when a patient with emphysema and cyanosis was given oxygen inhalations.

The viscosity-raising action of carbon dioxide we have demonstrated by rebreathing experiments.

A rubber mask, such as is used in giving gas anæsthesia, was closely fitted over the nose and mouth of a patient, and he was made to breathe over and over again the air contained in a four-liter rubber balloon. Rebreathing was continued until tachypnœa and cyanosis were pronounced, when the mask was removed. The viscosity of the blood determined just before, during and 30 minutes after the experiments are here tabulated:

Before rebreathing.	During rebreathing.	After thirty minutes.
4.5	4.8	4.6
3.7	4.4	3.9
4.2	4.6	4.2
4.6	4.9	4.7
3.9	4.3	4.0
4.0	4.5	4.2
4.3	4.6	4.3
4.5	4.6	4.5
4.8	5.0	4.8

In every instance the viscosity of the blood was increased during the experiments, to decrease again when normal air had been breathed for 30 minutes.

Conclusions.

1. The viscosity of the blood is a variable factor, determined to some extent by the variations in the constituent elements of that fluid.

2. It is slightly greater in men than in women.

3. The viscosity of the blood depends on the number of the red corpuscles, the hæmoglobin content, the gaseous richness; and to a lesser degree, on the proteid, fat and salt composition of the blood. With no one of these factors does viscosity vary in direct proportion.

4. The viscosity of the plasma is normally 1.7-2.0, average 1.86.

5. The viscosity of the blood is not influenced by diets used over short periods of time.

II. The Viscosity of the Blood in Disease.

When the influence on the viscosity of the blood, which the factors just cited exercise is recalled, it would seem probable that in those diseases in which the blood is most affected the maximal alterations in the viscosity would be found. It would seem likely for instance, that the readings would be low in

anæmia, high in polycythæmia; low in hydræmia, high in conditions with marked salt retention, and so on. To what extent this *a priori* reasoning is valid, the following observations show.

A. SECONDARY ANÆMIA.

Under this heading are collected anæmias of different degrees of severity occurring in diverse functional and organic diseases.

Disease.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity.
Ascaris lumbricoides	3,300,000	9,900	68%	3.2
Carcinoma of sigmoid	2,840,000	8,300	30	2.8
Carcinoma of rectum	2,530,000	13,000	28	2.4
Aortic aneurism	3,496,000	8,800	40	3.6
Aortic aneurism	3,620,000	9,500	44	3.7
Dementia paralytica	4,220,000	5,900	50	4.1
Tabes dorsalis	4,500,000	7,100	56	4.2
Malaria	3,700,000	5,100	40	3.5
Tuberculous peritonitis	2,600,000	10,600	30	2.4
Brain tumor	3,540,000	7,900	36	3.1
Myocarditis	2,320,000	7,160	56	1.8
Hysteria	3,900,000	6,800	60	3.2
Chronic nephritis	4,130,000	19,480	92	2.6
Chronic nephritis	4,480,000	6,000	76	4.4
Tuberculosis	2,200,000	4,600	62	3.6
Typhoid fever	4,320,000	6,100	70	4.4
Spastic paraplegia	3,648,000	9,000	51	3.6
Typhoid fever, convalescence.	4,272,000	8,100	76	4.2
Malaria	3,120,000	5,600	63	3.1
Syphilis tertiary	4,000,000	6,000	70	4.3
Carcinoma of stomach	2,700,000	11,000	50	2.9
Tuberculous meningitis	3,920,000	12,100	52	3.8
Typhoid fever	4,300,000	7,200	67	4.3
Typhoid fever	4,000,000	6,600	63	3.9
Dementia præcox	4,300,000	5,800	80	4.2
Hæmorrhoids	2,160,000	9,900	40	2.0
Neurasthenia	4,100,000	7,500	80	3.9
Psychasthenia	3,900,000	6,380	61	3.7
Gastric neurosis	4,320,000	8,100	73	4.2
Amœbic dysentery	4,200,000	9,600	67	4.2
Carcinoma of stomach	2,080,000	12,200	47	2.6
Myocarditis	3,610,000	11,400	44	3.7
Diabetes mellitus	3,600,000	7,600	64	3.6
Cirrhosis of liver	4,208,000	8,000	90	4.4
Cirrhosis of liver	3,870,000	9,200	81	3.7
Delirium tremens	4,180,000	10,100	70	4.1

From this tabulation it is evident that the viscosity of the blood is diminished in anæmic individuals, and that the diminution is roughly proportional to the severity of the anæmia.

Of no little interest is the gradual return of the viscosity towards normal with the onset of convalescence, a fact previously noted by Determann (*l. c.*) and beautifully shown in these two cases.

CASE I.

Date.	R. B. C.	Hæmoglobin.	Viscosity.
November 4	3,496,000	40%	3.6
November 11	3,620,000	44	3.7
November 18	3,900,000	39	4.0
November 25	4,220,000	50	4.0
December 2	4,520,000	59	4.4
December 9	4,900,000	81	4.5

CASE II.

Date.	R. B. C.	Hæmoglobin.	Viscosity
March 1	2,200,000	30%	2.5
March 8	2,300,000	30	2.5
March 15	2,500,000	32	2.7
March 22	3,000,000	38	3.1
March 29	3,450,000	40	3.3
April 6	4,100,000	51	3.7
April 13	4,000,000	60	3.8
April 20	4,650,000	78	4.3

B. PRIMARY ANÆMIA AND LEUKÆMIA.

I. Primary Pernicious Anæmia.

Case.	R. B. C.	Hæmoglobin.	W. B. C.	Viscosity. Blood.	Viscosity. Plasma.
1	1,950,000	40%	7300	2.0	1.5
2	780,000	43	8000	1.9	1.1
3	1,072,000	50	9200	2.3	1.3
4	2,225,000	61	6300	2.5	1.4
5	1,220,000	50	8700	1.7	1.2

II. Leukæmia.

Case.	Type.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma
1	Myelogenous	3,000,000	339,000	60%	6.2	2.4
2	"	2,800,000	76,000	58	3.9	1.8
3	"	3,600,000	40,000	65	4.7	2.0
4	Lymphatic	2,320,000	46,400	56	3.6	1.9

Table I shows that in primary pernicious anæmia, as in secondary anæmias, the viscosity of the blood is low, and here, too, the coefficient of the plasma is subnormal.

Table II, on the contrary, shows that in leukæmia, though the viscosity of the blood may be decreased, due probably to the marked anæmia, the readings are not as low as would be expected, and in some cases hyperviscosity may be noted. Rotky (*l. c.*) found similar changes and also noted an increased viscosity of the plasma. He finds an explanation for the relative and absolute high values in leukæmia in the marked leucocythæmia.

C. POLYCYTHÆMIA.

If conclusions can be drawn from the observations on the influence of erythrocytic and hæmoglobin richness of the blood on viscosity, these cases should show high coefficients, and in the four cases examined this was true.

Disease.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.	
Mediastinal tumor..	8,120,000	6,900	119%	13.6	2.9	Cyanosis.
Obesity	7,620 000	5,300	105	8.3	2.2	No cyanosis.
Osler-Vaquez disease	6,049,000	7,300	102	6.2	2.4	Cyanosis.
Emphysema	6,320,000	9,400	104	6.1	2.3	Cyanosis.

In all four the viscosity of the plasma was also increased, confirming the observation of Kottmann (*l. c.*).

D. NEPHRITIS.

Diagnosis.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.	Blood pressure.
Chr. nephritis	3,240,000	7,560	65%	3.2	2.1	220
Acute "	5,048,000	15,400	85	3.9	2.3	108
Chr. "	5,800,000	6,000	100	5.6	2.1	180
" "	4,300,000	6,200	80	3.9	2.0	180
Acute "	5,000,000	15,800	90	4.0	2.2	195
" "	5,120,000	11,400	99	4.3	2.4	173
Chr. "	3.640,000	9.300	60	3.8	2.1	140
" "	3,230,000	7,400	75	3.6	2.0	210
" "	2,000,000	5,900	63	3.2	2.1	192
" "	3,720,000	9,300	60	3.9	2.3	155
" "	3,500,000	7,000	59	3.8	2.0	198
" "	4,120,000	5,900	76	4.2	1.9	144
" "	4,700,000	8,300	81	4.3	2.1	150
" "	4,340,000	8,600	80	4.1	2.4	194
" "	4,600,000	7,300	79	4.4	2.0	187
" "	3,980,000	6,900	66	3.9	1.8	162
" "	3,820,000	7,900	69	4.0	2.0	155
Acute "	4,650,000	5,300	70	4.5	2.2	185
Chr. "	3,920,000	6,200	72	4.0	1.9	173
" "	5,000,000	7,100	90	5.1	2.3	148
" "	3,000,000	9,000	72	2.8	1.9	110
" "	3,120,000	5,400	55	3.2	1.7	151
" "	4,200,000	7,300	73	4.1	2.0	186
" "	4,750,000	6,500	77	4.3	2.1	192
" "	3,910,000	6,900	68	3.6	1.9	174
" "	3,300,000	7,800	62	3.7	1.7	139

In 22 of the cases the viscosity of the blood was subnormal, in two about normal, and in only two above normal. In 13, there was hypervicosity of the plasma, a normal coefficient in 13, and hypoviscosity in none. These statistics are in complete agreement with those of Rotky (*l. c.*)

The low viscosity of the blood probably finds its chief explanation in the anæmia present, while in a few instances it is not unlikely the result of hydræmia. As a further factor in bringing about hypoviscosity, Baehmann[19] considers globulin. He says "crystallizable bodies have a lower viscosity than non-crystallizable ones. Globulin belongs to the first group, and since in nephritis a relative globulin increase occurs, this condition may contribute to a reduction of viscosity." As to the cause of the hyperviscosity of the plasma, we may speculate on the presence of retained products of metabolism, perhaps protein, perhaps salt, their effects on the viscosity of the whole blood veiled by the greater influence of the formed elements, hæmoglobin, etc., but made clear when these are removed by centrifugation.

Interesting in connection with renal disease is the relation of the viscosity to blood pressure. In 18 of the cases there was hypertension (155-220 mm. Hg.), in two there was hypotension, and in six the tension was about normal. The study of the protocol of the cases shows that no constant relation exists—with hypertension there may be hypoviscosity or hyperviscosity and *vice versa*. Many of the patients with increased pressure, however, showed lowered viscosity of the blood, due perhaps, as Bachmann has suggested, to the indirect influence of hydræmia—"hydræmia leads to increased heart action and correspondingly to high pressure in order that, in spite of the thinning of the blood, the tissues may still be properly nourished."

E. CARDIAC DISEASE.

I. With Œdema.

Disease.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.	Remarks.
Myocarditis.	2,840,000	8,000	40%	2.9	1.3	Anasarca; no cyanosis.
Aortic and mitral insufficiency....	3,960,000	6,000	51	3.8	1.5	Œdema of legs; no cyanosis.
Mitral insufficiency.....	3,520,000	6,600	53	3.9	1.7	Ascites; œdema; no cyanosis.
Myocarditis.	4,200,000	7,800	69	4.4	1.8	Œdema of legs; no cyanosis.
Aortic and mitral insufficiency....	4,800,000	10,400	63	4.4	1.2	Hydrothorax; œdema of legs; no cyanosis.
Aortic insufficiency.....	3,120,000	8,900	48	3.6	1.3	Anasarca; hydrothorax.
Mitral insufficiency; myocarditis.	3,680,000	12,300	52	3.9	1.5	Anasarca; no cyanosis.
Mitral stenosis and insufficiency....	4,530,000	14,100	67	4.3	1.4	Moderate cyanosis.
Mitral insufficiency.....	4,670,000	9,600	69	4.9	1.6	Marked cyanosis.
Myocarditis.....	3,700,000	8,900	55	4.0	1.7	Œdema of legs; no cyanosis.

Hypoviscosity occurs in this series almost without exception. The low values are doubtless due in part to the anæmia, in part to the hydræmia. The latter probably stands in a causal relation to the diminished viscosity of the plasma.

II. Without Œdema.

Disease.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity.	Blood pressure.	Remarks.
Mitral insufficiency.....	4,792,000	9,800	82%	4.7	150	No cyanosis.
Aortic insufficiency.....	3,496,000	11,000	45	3.9	195	No cyanosis.
Mitral and aortic insufficiency ...	4,220,000	7,500	60	4.5	166	No cyanosis.
Myocarditis.....	4,520,000	10,200	58	4.7	180	Slight cyanosis.
Myocarditis.....	3,984,000	8,600	71	4.0	189	No cyanosis.
Mitral stenosis and insufficiency....	5,280,000	12,000	92	5.0	140	Marked cyanosis.
Mitral insufficiency.....	5,000,000	7,400	90	5.0	170	Marked cyanosis.
Myocarditis.....	3,620,000	6,600	53	4.2	210	No cyanosis.
Mitral stenosis and insufficiency....	5,400,000	9,500	93	5.2	185	Marked cyanosis.
Mitral insufficiency.	5,200,000	14.000	91	5.1	190	Marked cyanosis.

In this group no constant alteration in the viscosity values are found. The low readings correspond in the main with the anæmia, the high readings with the polycythæmia and the cyanosis. The blood-pressure viscosity ratio, as in nephritis, is inconstant, though occasional instances of association of low viscosity with high tension does suggest a compensatory mechanism.

F. DIABETES MELLITUS.

No.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.	Remarks.
1	4,930,000	7,200	91%	5.2	2.2	Young man, obese.
2	5,300,000	9,400	98	5.4	2.3	Young man, thin; acidosis.
3	5,640,000	6,900	100	5.9	2.3	Obese woman; acidosis.
4	4,520,000	8,600	89	4.3	1.7	Thin woman, young.
5	4,700,000	9,800	86	4.2	1.9	Obese woman, aet. 60.
6	5,000,000	7,700	92	4.8	1.8	Obese woman, aet. 42.

Three of the cases show increased viscosity of the blood and of the plasma—one shows high normal values, and in the remaining two, low readings for the blood, and normal ones for the plasma were obtained.

The increased viscosity of the blood is here probably due to the relative polycythæmia, the result of concentration of the blood due to the polyuria. As to the factors concerned in the production of hyperviscosity of the plasma, concentration, lipæmia, and hyperglycæmia all probably play a rôle. That lipæmia would raise the viscosity of the plasma is to be expected from the observation of Burton-Opitz (*l. c.*[13]) that "in dogs, food rich in fat raises the viscosity of the serum especially." The same observer found "inconsiderable" rises in viscosity in dogs with artificially produced hyperglycæmia.

G. JAUNDICE.

Diagnosis.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.
Cholelithiasis	5,100,000	14,300	94%	5.2	2.1
Cholelithiasis	4,900,000	19,200	90	5.0	2.0
Cholelithiasis	4,820,000	10,200	90	4.8	1.9
Carcinoma of bile ducts.	3,700,000	26,000	73	4.6	2.0
Carcinoma of pancreas..	2,920,000	9,400	58	5.3	2.4
Catarrhal jaundice	5,000,000	8,900	96	5.1	2.2
Catarrhal jaundice	4,780,000	14,000	86	4.9	2.0
Acute hepatitis	4,200,000	18,000	80	4.7	1.8
Luetic hepatitis	4,600,000	7,000	82	5.0	1.9

The high coefficient here is probably due to the cholæmia which was present in all of the cases.

II. ACUTE INFECTIOUS DISEASES.

I. Typhoid Fever.

The unusually large typhoid fever service in the Johns Hopkins Hospital furnished a long series of these cases in which any characteristic changes in the viscosity of the blood could be studied. The influence of restricted diet, of febrile reaction and of cold sponges and tubs could also be noted.

No.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity Blood.	$\frac{Hb}{V}$	Viscosity after sponge.	Remarks.
1	4,690,000	4,300	80%	4.8	16.6	5.0	1st week.
2	4,272,000	3,750	76	4.2	18.0	4.4	1st week.
3	4,120,000	5,100	70	4.0	17.5	4.2	2d week.
4	4,310,000	6,200	74	4.4	16.8	4.5	2d week.
5	4,000,000	3,600	69	3.9	17.7	3.9	2d week.
6	4,868,000	7,000	83	4.5	16.2	4.6	2d week.
7	4,236,000	4,600	80	4.1	19.5	4.2	3d week; furunculosis.
8	4,100,000	8,000	75	3.9	18.9	4.1	4th week; phlebitis-relapse
9	4,300,000	6,680	67	4.2	15.9	4.5	3d week
10	3,960,000	7,600	63	3.9	16.1	4.1	3d week; hemorrhage.
11	5,000,000	8,200	89	4.9	18.1	5.0 Tub 80°	1st week; psychosis.
12	4,860,000	4,300	84	4.7	17.8	5.0	2d week.
13	4,730,000	3,980	84	4.7	17.8	4.8	2d week.
14	4,120,000	4,600	82	4.0	20.5	4.4	2d week; bronchitis.
15	3,980,000	3,700	76	4.2	18.0	4.3	1st week; bronchitis.
16	4,980,000	5,100	91	5.0	18.2	5.0	2d week.
17	4,530,000	5,420	88	4.5	19.5	4.9	2d week; phimosis.
18	4,420,000	6,200	83	4.3	19.3	4.5	2d week.
19	4,500,000	6,700	81	4.5	18.0	4.7	2d week.
20	4,720,000	6,300	86	4.8	17.9	4.9	2d week.
21	4,930,000	3,570	89	5.0	17.8		3d week.
22	4,460,000	4,680	80	4.5	17.7		3d week.
23	4,570,000	4,000	83	4.3	19.3		3d week.
24	5,080,000	6,600	95	5.0	19.0		1st week.
25	4,000,000	7,400	79	4.0	19.7		2d week.
26	4,800,000	9,000	86	4.6	18.7		3d week.
27	4,880,000	8,300	90	4.9	18.4		3d week.
28	4,240,000	6,700	82	4.1	20.0		3d week.
29	4,590,000	5,900	86	4.2	20.4		3d week.
30	4,780,000	7,100	83	4.5	18.4		3d week; cholecystitis.
31	4,630,000	8,500	85	4.5	18.8		3d week.
32	4,690,000	11,100	83	4.0	20.7		3d week.
33	4,760,000	10,300	81	4.1	19.7		3d week.
34	4,511,000	9,700	79	3.9	20.2		4th week.
35	4,316,000	8,800	79	4.0	19.7		4th week.
36	4,920,000	6,900	84	4.4	19.0		4th week.
37	4,130,000	7,600	80	4.0	20.0		4th week; relapse.
38	3,895,000	8,040	76	4.0	19.0		4th week; hemorrhage 12th day.
39	5,400,000	3,750	92	4.2	21.9		4th week; well.
40	4,540,000	6,000	80	4.2	19.0		4th week; well.
41	4,290,000	5,700	77	3.8	20.2		4th week; well.
42	4,730,000	10,000	87	4.3	20.2		4th week; well.
43	3,960,000	4,600	74	3.8	19.5		4th week; epistaxis.
44	3,820,000	4,900	76	3.8	20.0		4th week; emaciated.
45	5,000,000	6,800	93	4.6	20.2		4th week; well.
46	5,130,000	3,200	93	5.0	18.6		6th week; well.
47	4,660,000	4,980	88	4.8	18.3		6th week; well.
48	4,620,000	6,600	87	4.5	19.3		5th week; well.
49	3,980,000	7,300	84	4.0	21.0		8th week; well; perforation.
50	4,320,000	4,160	74	4.3	17.2		7th week; cholecystitis; well.

From these data the following conclusions may be drawn:

1. Typhoid fever produces no characteristic change in the viscosity of the blood.

2. The lowered values noted during the course of the disease with later gradual restitution to normal as convalescence progresses, is parallel to the development of anæmia and the subsequent regeneration of the blood.

3. The hæmoglobin—viscosity quotient $\left(\frac{Hb}{V}\right.$, which Bachmann (*l. c.*) has shown to be increased in this disease, varies considerably, and in the majority of instances is subnormal, in one patient being as low as 16.0 (normal=20). This author had found a high quotient in 10 out of the series of 11 cases, and having noted a subnormal quotient in pneumonia, stated that—"these few observations show that a differential diagnosis between these diseases can readily be made by a comparison of their quotients." In this we do not concur.

4. Cold sponges or tubs, whether followed by a good reaction or by cold and shivering, cause an elevation of viscosity. This is in agreement with the observations of Determann (*l. c.*[8]).

5. The restricted diets—consisting of milk, albumen and mush—apparently have no marked effect on the viscosity of the blood.

6. The leucopenia is apparently of no importance in this connection.

II. Pneumonia.

In pneumonia the occurrence of marked salt retention and of cyanosis would, other things being equal, lead to increased viscosity of the blood. Leucocytosis is rarely so marked as to enter into consideration as a factor.

Remarks.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity.	Hb / V
Crisis. Rt. lung	4,240,000	19,240	71%	4.3	16.5
Crisis. Rt. lower lobe	4,900,000	26,000	78	4.6	16.9
Rt. lung. Empyema	5,220,000	42,000	96	5.5	17.4
Lt. lung. Empyema	5,010,000	32,000	93	5.1	18.2
Rt. lung and Lt. lower lobe	5,100,000	20,000	90	5.2	17.2
Both upper lobes	4,600,000	16,400	80	4.9	16.3
Lysis. Rt. lower lobe	4,720,000	12,300	78	4.8	16.3
Crisis. Rt. lower lobe	4,490,000	14,300	72	4.6	15.6
Crisis. Rt. upper lobe	4,700,000	10,200	76	4.9	15.9
Both lower lobes	5,000,000	19,300	84	5.2	15.4
Rt. upper lobe pleural effusion	5,600,000	22,200	96	5.9	16.3
Rt. lower and middle and Lt. lower lobes.	3,900,000	11,600	65	4.7	17.8
Lysis. Rt. lower lobe	5,430,000	13,400	94	6.0	15.6
Both lower and Rt. upper lobes	3,800,000	18,300	67	3.9	16.0
Lysis. Rt. upper lobe	4,750,000	28,000	75	4.9	15.3
Crisis. Lt. lower lobe	4,240,000	21,000	72	4.0	18.0
Crisis. Rt. lower lobe	4,160,000	16,000	72	4.3	16.7
Lysis. Rt. lower lobe	3,920,000	14,600	66	4.0	16.5
Crisis. Rt. lung	4,804,000	17,100	82	5.0	16.4
Crisis. Rt. lower lobe	4,920,000	12,000	88	4.7	18.6

Thirteen of the cases showed increased viscosity of the blood and in all the hæmoglobin-viscosity quotient was diminished. The latter finding is more constant than in typhoid fever, but from it no safe inference can be drawn.

III. Malarial Fever.

No.	R. B. C.	W. B. C.	Hæmoglobin.	Viscosity. Blood.	Viscosity. Plasma.
1	3,800,000	5500	65%	3.9	2.1
2	4,300,000	6400	80	4.4	1.9
3	4,700,000	5900	82	4.9	2.4
4	4,100,000	7900	74	4.2	2.2
5	3,300,000	8100	68	5.0	2.0
6	4,520,000	6800	72	4.3	1.8
7	4,600,000	5200	76	4.5	1.9
8	4,200,000	4900	70	5.2	2.0
9	4,900,000	5900	85	4.5	2.0
10	4,700,000	7300	81	4.6	1.9

Here there is either normal or subnormal viscosity of the blood, and normal or hypernormal viscosity of the plasma. The lowered readings for the blood where present, are probably due to the anæmia, and the high readings in three of the cases may find an explanation in the increased volume of the infected erythrocytes. The high viscosity of the plasma may be the result of hæmoglobinæmia present in these cases.

CONCLUSIONS.

The viscosity of the blood and of the plasma is reduced in anæmias, either primary or secondary. With regeneration of the blood, normal values are restored. In leukæmia there is hypoviscosity of the blood with hyperviscosity of the plasma. Leucocythæmia may explain the hyperviscosity of the blood, which is found in a few cases.

The viscosity of the blood and of the plasma is increased in polycythæmia.

Hypoviscosity of the blood and hyperviscosity of the plasma is almost constant in cases of nephritis; the former due to the anæmia, the latter to retained products of metabolism. Though in many instances hypoviscosity occurs in cases with hypertension, this interrelation is often absent.

In cardiac disease without œdema, no constant change is the viscosity is to be found, the coefficient apparently varying with the anæmia and the carbon dioxide content of the blood. In cases with hydræmia, there is hypoviscosity of the plasma.

In diabetes mellitus, the viscosity of the blood and of the plasma is increased, in many cases probably the result of concentration of the blood due to polyuria, of hyperglycæmia and of lipæmia.

In icterus there is generally increased viscosity of the blood and in the plasma, probably the result of cholæmia.

In typhoid fever the viscosity varies with anæmia, is increased by hydrotherapy, and apparently is uninfluenced by diet. The $\left(\frac{Hb}{V}\right)$ quotient is more often decreased than increased.

In pneumonia the viscosity is generally above normal due to cyanosis and salt retention. Here, too, the $\left(\frac{Hb}{V}\right)$ quotient is low.

In malarial fever the viscosity of the blood is usually normal or subnormal, rarely above normal. The viscosity of the plasma is normal or increased, the last as a result of hæmoglobinæmia.

In no disease studied could a pathognomonic alteration in the viscosity of the blood be demonstrated.

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SARCOMA AND TUBERCULOSIS.

REPORT OF A CASE.

By J. P. SIMONDS, M. D.,

Superintendent, Laboratory of Bacteriology and Pathology, Indiana State Board of Health, Indianapolis.

Rokitansky,[1] in 1846, declared that tuberculosis and carcinoma are very infrequently found occurring in the same patient. He even believed the two conditions were almost incompatible, and tabulated his reasons for this opinion. A few years later, Lebert[2] disputed Rokitansky's statement because he found 15 cases of tuberculosis among 173 patients with carcinoma. He believed that a patient with cancer could contract tuberculosis as well as any one else, but considered the occurrence of carcinoma in the progress of tuberculosis rare.

These observations stimulated the reporting of cases of carcinoma associated with tuberculosis, so that to-day the literature on that subject is quite abundant. The association of sarcoma with active tuberculosis seems to have been observed very much less frequently. An examination of the post mortem records of about 2500 cases of sarcoma of various organs collected from the literature yielded 19 which showed this combination. In about 100 other cases the tuberculous process was not active.

The cases found in the literature may be grouped in three classes. In the first, the tumor and tuberculosis are primary in the same organ in which the two processes may be either separate or intermingled. Secondly, sarcoma and tuberculosis are primary in adjacent organs and the tumor may or may not grow into the one with tuberculosis. In the third group the lesions are primary in remote organs and there may or may not be sarcoma metastases in the tuberculous organ.

Hildebrand[3] and Schick[4] each reported cases of primary sarcoma of the lung associated with pulmonary tuberculosis. In the former's case the two processes were intermingled. Clement[5] observed an endothelioma of the parotid gland and the entire region of the lower jaw with a focus of tuberculosis near the center of the tumor. In two cases of lymphosarcoma of the intestine reported by Störck[6] and Franco,[7] the tumor and tuberculosis were intimately associated. Freudweiler[8] found tuberculous caseation and lymphosarcoma in the same lymph gland removed at operation. Mueller and Ricker[9] removed a small sarcoma from a breast. Later two nodules appeared in the scar, one sarcomatous the other tuberculous. Tauffer[10] excised an epithelioma which had developed on a lupus lesion, and a mixed spindle-giant-celled sarcoma developed in the scar.

Pulmonary tuberculosis associated with sarcoma of the mediastinum has been observed by Harris,[11] Fowler and Godlee,[12] and Bushnell and Broadbent.[13] In Harris' case the tumor also involved the left lung. Ricker[14] reported a lymphosarcoma of the cervical glands with tuberculosis of the adjacent lymph nodes. An endothelioma of the pia arachnoid of the lumbar cord with tuberculosis of the lumbar vertebræ was reported by Dufour.[15] Bobbio[16] described a spindle-celled sarcoma following three operations on a fistula caused by a tuberculous scapula.

Retroperitoneal sarcomas associated with tuberculosis of the lungs have been reported by Phillipson[17] and McCallum.[18] In the latter's case there were metastases in the lungs. Jscovesco[19] reported a case of tuberculosis of both lungs with sarcoma nodules on the pleura. The site of the primary tumor was not stated. Lazarus-Barlow,[20] in 121 cases of sarcoma, found two associated with active pulmonary tuberculosis. The primary tumor in one case was an endothelioma of the tongue with no metastases; in the other, a round-celled sarcoma of the ischiorectal fossa with metastases in the lungs and other organs.

In addition to the above 19 cases, Rapok[21] has analyzed 141 sarcomas operated on at the Strassburg Surgical Clinic. Among them he found 15 cases associated with tuberculosis. There were 669 tumors of all kinds treated during the same period and 66 of the patients also had tuberculosis. In Rapok's series, the percentage of patients with sarcoma showing tuberculosis was a little higher than the average for all tumors.

Bang[22] analyzed all the cases with tuberculous lesions that came to post mortem at the Commune Hospital in Copenhagen in the 10 years from 1886 to 1895. During this period 6006 autopsies were done and of these 2340 showed tuberculosis in various stages in some part of the body. He found 54 true sarcomas and 34 brain tumors (some of which were probably sarcomas), with which some tuberculous lesion was associated. But in no case was the tuberculosis active.

The following case was first seen by the author at the autopsy table. For the clinical history he is indebted to the house physicians of the St. Louis City Hospital:

The patient was a negress about 60 years old. The family and personal history were negative. When admitted to the

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[1] Lehrbuch der allgemeinen Pathologie, Wien, 1846, Erste Auflage, Bd. 1, S. 424, u. 552.

[2] Virchow's Arch., 1852, IV, 214.

[3] Inaug.-Diss., Marburg, 1887.

[4] Inaug.-Diss., Greifswald, 1890.

[5] Revue de la tuberculose, 1895, III, 134; quoted by Franco, l. c.

[6] Sitzungsberichte der k. k. Gesellschaft der Aerzte in Wien, 1895. Abs. in Lubarsch and Oestertag's Ergebnisse, 1898, V. 214.

[7] Virchow's Arch., 1908, CXCIII, 377.

[8] Quoted by Franco, l. c.

[9] Quoted by Franco, l. c.

[10] Virchow's Arch., 1898, supplement to Bd. CLI, 272.

[11] St. Bartholomew Hosp. Rep., 1892, XXVIII, 87.

[12] Diseases of the Throat and Chest, London, 1898, p. 684.

[13] Jour. Path. and Bact., 1909, XIII, 204.

[14] Quoted by Franco, l. c.

[15] Quoted by Franco, l. c.

[16] Giornal della R. accad. di Med. de Torino, 1906, XII, Series 4, p. 452.

[17] Lancet, 1885, I, 937.

[18] Trans. Assoc. Amer. Physicians, 1907, XXII, 391.

[19] Quoted by Franco, l. c.

[20] Arch. Middlesex Hosp., 1904, II, 224, and 1906, VII, 17.

[21] Deutsche Zeitschr. f. Chirurg., 1889-90, XXX, 465.

[22] S. Bang, Tuberkulosins Sammentraef med forskellige andre Sygdomme belyst ved 6006 Sektionsfund, Copenhagen, 1901.

hospital, November 20, 1907, she was emaciated almost to the last extreme. Her temperature was normal, pulse 70, and respiration 26.

The present trouble began two months before admission, when she first noticed a swelling in the epigastrium. It seemed as if food would not pass this point. She lost weight rapidly from the first. About two weeks after she first noticed the swelling, she vomited twice in one day, the first time, a large amount of greenish material, and a few hours later, almost pure blood. She had not vomited since that time. Ascites developed, and during the last seven weeks, she had been tapped three times.

On physical examination, the sclera were white. The heart and lungs showed nothing abnormal. A hard, irregular mass was felt in the epigastrium, being especially prominent to the right of the middle line. What was thought to be the spleen, could be palpated two inches below the costal border in the left anterior axillary line. The abdomen contained much free fluid, which, together with the extreme weakness of the patient, and marked abdominal tenderness, rendered thorough physical examination impossible. The urine contained a trace of albumin, but otherwise showed nothing abnormal. Blood examination revealed a leucocytosis of 34,000 of which 90 per cent were polymorphonuclears, 3,500,000 red cells, and 56 per cent hemoglobin.

The case was diagnosed carcinoma of the stomach.

Patient died on the eighth day after entering the hospital.

The post mortem examination was made about three hours after death.

Anatomical diagnosis: Retroperitoneal sarcoma; tuberculosis of the peritoneum and retroperitoneal lymph glands; chronic aortic endocarditis; atheroma of the aorta; chronic interstitial nephritis; miliary tubercules in the kidneys; atrophy of the spleen.

The body is that of a very old negro woman. Emaciation is extreme. Over the coccyx is a bed sore 1 cm. in diameter. The inguinal glands and one left supraclavicular gland are palpable.

The peritoneal cavity contains 2500 cc. of yellowish, slightly turbid fluid. The great omentum is short, rolled up and adherent throughout most of its length to the descending colon. The diaphragm is partially adherent to the anterior surface of the right lobe of the liver. Adhesions are present between the tip of the left lobe of the liver and spleen. Similar adhesions between subdiaphragmatic peritoneum and spleen enclose a multilocular cavity containing fluid similar to that in the general peritoneal cavity.

The visceral and parietal peritoneum are thickly studded with semi-translucent nodules (tubercles) miliary in size and larger, many of which are confluent. They are most numerous posteriorly between the lower border of the ribs and the crest of the ilium, and in the pelvis. Here the peritoneum is deeply congested. Thin velamentous adhesions stretch from the uterus to the adjoining structures, forming a complete roof over the cul-de-sac of Douglas. These nodules are fewest in number on the posterior surface of the stomach.

Three large tumor masses are visible on opening the peritoneal cavity. The first projects beyond the anterior border of the liver immediately to the right of the gall bladder; the second has grown between the stomach and the transverse colon; and the third projects from under the left costal border in the mammillary line. These masses are parts of a large irregular growth from the posterior abdominal wall between the liver and the root of the mesentery. Superiorly, it is attached to the gall bladder, and to the posterior part of the inferior surface of the liver to the left of the gall bladder. Posteriorly, the tumor lies in direct relation with the right kidney, vena cava, aorta, renal vessels, adrenals and left kidney, being adherent to the latter over the medial half of its anterior surface. On the left, it is adherent to the spleen, diaphragm and splenic flexure of the colon. Immediately inferior to it are the transverse colon, root of the mesentery, and duodeno-jejunal flexure. The transverse colon has been pushed downward in the middle line, but passes upward to the left of the mass in direct contact with, and adherent to, the descending colon to form the splenic flexure which is thus made a very sharp angle. The duodenum passes around the right border of the mass and, in its lower part, by turning backward and downward comes to lie somewhat between the growth and the right kidney. Anteriorly the central portion of the tumor is covered by the stomach, a small part of the duodenum, the gastro-colic omentum and the pancreas.

The pancreas has been pushed forward and upward so that it is no longer in direct relation with either the duodenum, portal vein or spleen. The head lies over the right margin of the growth and measures 2 cm. in its thickest part. The body and tail are stretched upward and to the left over the most prominent part of the growth. The pancreas is definitely separated from the tumor by a capsule.

On cut surface the appearance varies in different parts of the mass. That nearer the spinal column is firmer in consistency than the more superficial part. The color varies from pale yellowish-white to red and purple. Hemorrhages into the tumor are numerous especially in the left half of the mass immediately beneath the peritoneum. The tumor tissue is everywhere soft and friable; in the superficial hemorrhagic areas it is semi-fluid.

Several important structures lie well within the mass. The branches of the cœliac axis are surrounded by tumor tissue, especially the splenic and hepatic arteries. These vessels stand open on section. The course of the portal vein is tortuous, and it is separated from the head of the pancreas by tumor tissue 1 cm. in thickness. The common bile duct is completely surrounded but is patent and bile is easily pressed from the gall bladder into the duodenum.

There is some thickening of the mitral valve. The attached borders of the aortic cusps are calcified and the cusps themselves thickened. In the coronary arteries are numerous atheromatous plaques. The thoracic and abdominal aorta and the common iliac arteries contain numerous atheromatous plaques.

In the apex of the lower lobe of the left lung is a pin-head-

sized partially calcified nodule. The anterior borders are emphysematous. Otherwise the lungs show nothing noteworthy.

The palpable, left supraclavicular gland contains several miliary yellowish-white nodules. The tracheo-bronchial glands are anthracotic and very slightly enlarged. Lying posterior to the œsophagus 2 cm. above the diaphragm, is a gland the size of a small almond, which, on cut surface, shows a soft, white dstinctly limited area 3 mm. in diameter. The spleen is atrophied and its capsule covered with tags of adhesions.

The gastric mucosa is covered with thick blood-stained mucus. In the middle third, especially on the posterior wall, are a dozen or so pin-head-sized ulcers, each containing a small blood clot and extending 1 to 2 mm. into the mucosa. The contents of the intestines are blood tinged in the upper part and black and tarry in the region of the ileocœcal valve and below. Sixty-five centimeters below the duodeno-jejunal flexure, in the attached border of the intestine and extending into the mesentery is a mass 6.5 x 2.5 x 4 cm. It is firmly attached to the wall of the intestine and cannot be peeled off from it. The mass is soft, yellowish-white on cut surface, is very friable and contains two small irregular cavities containing necrotic material.

In the liver are a number of metastases from 0.5 to 1 cm. in diameter. The gall bladder contains dark green bile and numerous soft, small, black stones.

On cut surface both kidneys are red in color, the cortex measures 3 to 5 mm. in thickness and the cortical markings are indistinct. The capsule strips easily, leaving a finely granular surface. On the posterior surface of the left kidney there is one, of the right kidney two pin-head-sized, yellowish-white, opaque nodules. The interior of the urinary bladder is normal in appearance.

In the right ovary there is a small cyst 1.5 cm. in diameter, containing clear fluid. The left ovary is atrophied. The Fallopian tubes are normal except for the tubercles on their peritoneal surface. The uterus is small and its walls contain numerous small interstitial fibroids. The peritoneal surface is thickly covered with confluent tubercles. The cervix shows the results of a lateral tear. No evidence of primary tuberculosis of the genitalia can be discovered.

(The organs of the neck and the brain were not removed.)

Microscopical examination shows the large retroperitoneal tumor to be a typical spindle-celled sarcoma. The tumor mass at the insertion of the mesentery to the small intestine is similar in every respect to the larger growth. Sections cut to determine the relation of the smaller tumor to the wall of the intestine show that in the peripheral part both muscular layers separate the sarcoma from the submucosa. Toward the center the longitudinal muscle fibers, and still further on the circular fibers, completely disappear and the tumor is separated from the submucous layer only by a thin capsule. The muscular coat is not involved in the neoplasm. It has the appearance of having been bevelled off from without inward toward the submucosa and is always separated from the tumor by a thin capsule.

The small nodules in the peritoneum are characteristic tubercules. Many of the sections from the peripheral part of the large retroperitoneal tumor show a narrow rim of lymphatic tissue. In this zone numerous tuberculous foci are found with areas of necrosis and giant cells. The tuberculosis seems to be limited to the remaining retroperitoneal lymphatic structures. In no section has the sarcoma tissue itself been found infected. In the postœsophageal gland, in addition to the metastatic sarcoma, there are two or three very small foci of tuberculosis, but the two processes are always separated. The supraclavicular gland contains tubercules.

Tubercle bacilli were found in a number of sections cut so as to include the zone of lymphatic tissue on the surface of the large retroperitoneal growth.

The chief interest of this case lies in the association of a very rapidly growing retroperitoneal sarcoma with a very virulent tuberculous infection of the peritoneum. It was not possible to determine which condition appeared earliest. The fresh appearance of the tubercules and the exceedingly rapid growth of the sarcoma make it probable that both processes began about the same time. No source of origin of the tuberculous peritonitis could be found although searched for diligently. There were no tuberculous ulcers in the intestine, and the only tuberculosis of the genital organs was on their peritoneal surfaces. The fact that tubercles were more numerous and more often confluent in the pelvic peritoneum may have been due to the effect of gravity in causing the infected peritoneal fluid to collect there.

Of the above 130 cases,[23] tuberculosis was active in 34. Of the 20 cases (including the one here reported) in which sufficient data were given to permit their use in an analysis, tubercle bacilli were actually demonstrated in only 9 and not mentioned in 11. This is an important desideratum since Baty-Shaw [24] has reported a case of sarcoma of the mediastinum associated with pseudo-tuberculosis of the left lung. Grossly, the lesion in the lung closely resembled true tuberculosis, but the bacilli could not be found either in the contents of the cavities nor in sections of the lung.

That sarcoma and tuberculosis are rarely found in the same patient is an admitted fact, but that there is anything incompatible in the two conditions does not appear probable. The case here reported of a very virulent form of both diseases in the same patient would seem to be sufficient to preclude their being incompatible. There is no apparent reason why a tuberculous process should, by chronic irritation, cause the development of a sarcoma, although the cases of Bobbio and Tauffer rather remotely suggest such a possibility. Both of these cases had been operated upon two or more times previous to the appearance of the tumor. Taylor and Teacher [25] have reported cases in which a cancer appeared to cause the de-

[23] If we exclude Bang's 34 cases of brain tumor, some of which were undoubtedly not sarcomatous, the total will be 96 instead of 130.

[24] Brit. Med. Jour., 1901, 1, 1331.

[25] Jour. Path. and Bact., 1909, XIV, 205.

velopment of a sarcoma in the adjacent connective tissue. On the other hand, the general debility and consequent loss of resisting power which accompanies the growth of a sarcoma would prepare the soil for an infection with tuberculosis.

The following are suggested as possible reasons why the two lesions are not more frequently found associated: (1) The age incidence of the two diseases is not quite the same. Sarcoma and tuberculosis affect all ages, but the former is more frequent before 20 and the latter after that age. (2) The rapidly fatal course of a sarcoma may attract attention to itself so completely that the presence of a mild tuberculosis would not be recognized clinically.

CARCINOMA OF THE RIGHT FALLOPIAN TUBE READILY PALPABLE THROUGH THE ABDOMEN.

By Thomas S. Cullen, M. B.,
Associate Professor of Gynecology, Johns Hopkins University.

Cancer forms a very small percentage of the pathological conditions of the Fallopian tube. As pointed out by Hurdon,[1] carcinoma was noted only three times in the tube, as compared with some four hundred cases of cancer of the uterus that came under our observation in the Johns Hopkins Hospital. Among the more important American articles on this subject are those of LeCount[2] and Hurdon.[3] In the Johns Hopkins Bulletin of 1905, Vol. XVI, p. 399, I reported a case of adeno-carcinoma of the tube in which as a result of extensive involvement of the pelvic peritoneum and of the surrounding tissues I found it necessary to remove not only the entire uterus with the adnexa but also several inches of the sigmoid flexure and about one-third of the pelvic peritoneum.

Alban Doran,[4] of London, has given a complete survey of the literature and collected in all sixty-two cases. A further admirable monograph on the same subject by the same author[5] appeared a few months ago. In this the number of cases of carcinoma of the tube had been increased to one hundred.

After such thorough presentations of the subjects as have been furnished by these authorities a further survey of the literature would be simply a repetition and I shall merely report a case which came under my observation in the laboratory. Its chief interest lies in the large size of the growth. When I first saw the hardened specimen before learning the clinical history, I considered it to be a very large hydrosalpinx or pyosalpinx. On section, however, its true character was readily discernible.

Adeno-carcinoma of the right Fallopian Tube, extension to left Fallopian Tube; very small uterus.

San. No. 2453.—Mrs. M. H., aged 46. Admitted to Dr. Kelly's private sanitarium on May 14, 1907. The patient entered complaining of a mass and great pain in the lower part of the abdomen. The family and past history were negative.

The menses began at 14, were regular, moderate in amount, somewhat painful and usually lasted four days. For the last two or three months the periods have been irregular but profuse. She had one miscarriage when 18. Recently there has been a profuse leucorrhœal discharge which, for the past year, has been associated with some odor and with blood.

Present Illness.—Two years ago the patient first had what she called an attack of appendicitis. The pain was located in the right iliac fossa and was severe and cramp-like in character. It has persisted in this region and for the last year has also been present in the left side. The pain radiates into the leg and for the last four or five months both legs have been swollen.

Operation.—The uterus was removed by bi-section; a small piece of intestine was also removed on account of a little sub-peritoneal cyst which was supposed to be secondary to the tubal growth. There was no glandular involvement and no evidence of any peritoneal implantation.

Path. No. 11536. The specimen consists of a small uterus, of a greatly enlarged right Fallopian tube and of an enlarged left Fallopian tube.

The body of the uterus is 4 cm. long and about 4 cm. broad. It is markedly atrophied. The right tube at the uterus is about 7 mm. in diameter, but after passing outward 1 cm. it curves on itself, becomes markedly convoluted and 5 cm. from the uterus is 5 cm. in diameter. It continues to increase in size until at its outer end it is 10 cm. in diameter. Roughly it forms a sausage-like tumor 14 cm. long, 12 cm. broad, and about 10 cm. in thickness. Anteriorly it is covered with adhesions. Posteriorly it is perfectly smooth and springing from its surface is a sub-peritoneal cyst 1.5 cm. in diameter. Large congeries of blood vessels are seen ramifying beneath the peritoneum.

On section it is seen that the great increase in size is due in a large measure to a new growth. This has extended into the lumen of the tube, but at no point does it appear to have reached the outer surface. Where the tube is 5 cm. in diameter the growth completely fills the lumen. It is composed of a granular-looking new growth which presents a somewhat arborescent appearance. The growth apparently springs from all parts of the wall of the tube. Near the fimbriated extremity, where the tube is 10 cm. in diameter, for over fully half of its extent the walls are covered with a new growth. This in places reaches 2 cm. in thickness. At other points the tube seems to be free from the growth. The entire central portion of the tube has been filled with fluid that has undergone coagulation in the hardening fluid. In the fluid next the growth here and there are large blood clots. The gross picture leaves little doubt that we are dealing with a malignant growth. If it be malignant the reason why it has not extended outside seems evident, because the point of least resistance would be toward the center of the tube.

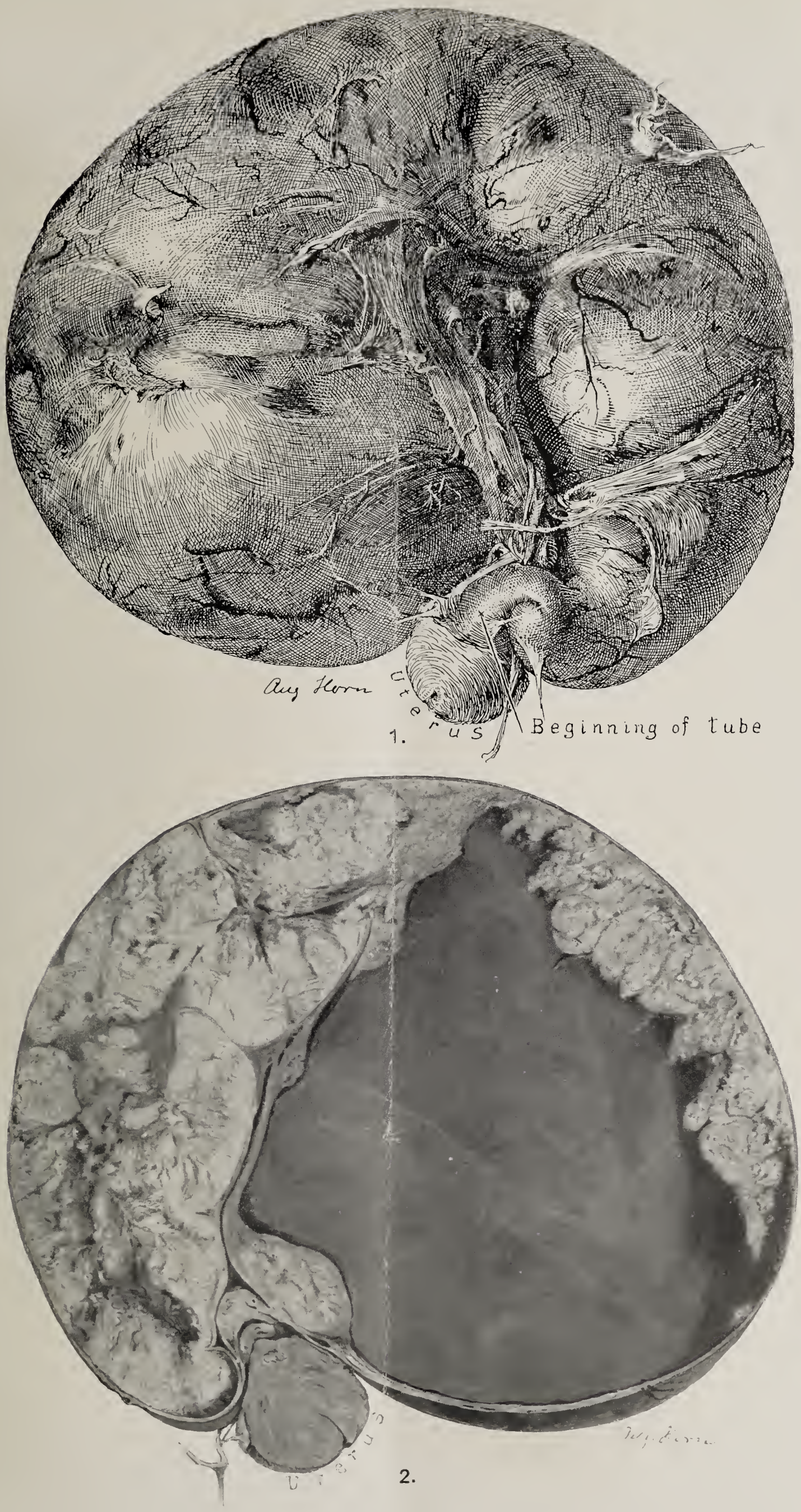
[1] Elizabeth Hurdon, Kelly, H. A., and Noble, C. P. Gynecology and Abdominal Surgery, Phila., 1907-08, I, 175.

[2] LeCount. Johns Hopkins Hosp. Bull., 1901, Vol. XII, p. 55.

[3] Elizabeth Hurdon. Johns Hopkins Hosp. Bull., 1901, Vol. XII, p. 315.

[4] Alban Doran. J. Obst. & Gynæc. Brit. Emp., Lond., 1904, VI, 285.

[5] Alban Doran. J. Obst. & Gynæc. Brit. Emp., Lond., 1910, XVII, 1.


Beginning of tube
1.
2.

The left tube, near the uterus, is 5 mm. in diameter, but on passing outward a short distance it is dilated to 4 or 5 cm. It likewise on section is found to be the seat of a similar growth. The tube is covered with adhesions.

Histological Examination.—Sections from the growth of the right tube show in some areas little tree-like or teat-like projections extending into the cavity. They remind one very much of the small folds noted where a hydrosalpinx exists. At other points the epithelium has proliferated forming gland-like areas. In more advanced portions over wide areas papillary outgrowths are seen. These present a distinct arborescent appearance and the projections are covered with one or several layers of very high, exceedingly regular cylindrical epithelium. Over large areas there is not the slightest evidence of breaking down. In still other portions of the growth one sees nuclei two or three times the usual size. These stain somewhat deeply. In other portions cross and longitudinal sections of finger-like processes with large blood vessels in their interior are seen. Here and there the epithelium proliferated until solid masses of glands have been formed. Masses of epithelium without evidence of gland formation are also noted. In only a few places is there evidence of breaking down.

The growth is, without doubt, a carcinoma, but is characterized by a marked tendency toward gland formation and papillary outgrowths, and by its stability instead of its tendency toward breaking down. One might, with some propriety, claim that it resembles, to a marked degree, a very cellular and branching papilloma.

It is interesting to note that the other tube presents a similar appearance. One tube may have picked the carcinoma up from the other. The tube walls themselves are not over 1 mm. in thickness. We did not receive the ovaries or the small nodule from the bowel for examination.

We find no record of any other carcinomatous tube that has reached such large proportions.

Post-Operative History.—Sept. 30, 1910. Dr. Curtis F. Burnam kindly made inquiry concerning the patient and finds that there is at present a marked recurrence of the growth, there being a large palpable abdominal mass. The patient, however, is able to do her work most of the time and her general health has been but little affected.

The growth has evidently been a rather slow one as it is nearly three years and a half since operation.

DESCRIPTION OF FIGURES.

FIG. 1.—Primary Carcinoma of the Fallopian Tube. (Natural size.)

The small uterus has been bisected and one-half is seen in the lower part of the picture. The tube at the cornu is small, but after passing outward a short distance rapidly increases in size. Its outer end is so much distended that it might readily be mistaken for an ovarian cyst. The surface of the tube is covered by numerous adhesions and its vessels are large and tortuous. The interior of the tube is shown in Fig. 2.

FIG. 2.—Primary Carcinoma of the Fallopian Tube. (Natural size.)

For the general contour see Fig. 1. In the lower part of the picture is a cross section of half of a bisected uterus. The great increase in size of the tube is in a large measure due to a friable, stringy growth which almost completely fills the lumen. The great distension of the outer end of the tube has been caused by an accumulation of serous fluid which has coagulated in the hardening fluid. This coagulum is seen retracting from the tube wall and could readily be lifted out of the tube in one piece. It will be noted that where the tube is so much dilated its walls over a considerable area are totally devoid of new growth.

IN MEMORIAM.

AUGUST HORN.

On August 19, 1910, our friend and associate, August Horn, died suddenly in Bad Nauheim, where he had gone in quest of health. He had been ill for nearly a year with post-typhoid myocarditis and many of the distressing secondary affections peculiar to this disease. He was buried in Leipzig-Mockau, where his invalid father and mother still live. He was an only son, the pride of humble parents.

Horn's artistic ability asserted itself early, and in 1884 at the age of 15 years, he entered the "Königliche Kunstakademie und Kunstgewerbeschule" in Leipzig, where he devoted his time to the study of the fine arts and, as it was customary in those days in Leipzig's academy, he also took up one of the graphic arts, viz., lithography. This was done to assure himself of a livelihood in case his talent should prove insufficient for creative work. This step I consider fortunate as will appear later. He was always very conscientious and came to excel in all tasks which required a combination of artistic feeling with a high degree of technical skill. On the other hand, in the study of the theory and science underlying art, Horn showed less enthusiasm. But his instinct usually supplied what his mind did not grasp and so well did he observe and analyze that he rarely showed in his work the lack of theoretical study.

The comparative narrowness of artistic ideals in Leipzig caused Horn to become a student in Munich, where he painted for a number of years under several well-known masters. Through his colleagues he became known to wealthy art connoisseurs, and since the life of a poor artist, in a center like Munich, is one of great deprivations, he turned aside, temporarily at least, to become a copyist. He was sent to Dresden, Venice, Milan, Rome and other places with orders to copy famous works of the old masters. These copies were exceedingly well done, faithful even to the technical peculiarities characteristic of each master.

Such was his work when I visited Leipzig in 1898. Having been requested to suggest an artist for Dr. Halsted and his department, if one such could be found, I at once thought of Horn and induced him to give up his work in Italy and become a medical illustrator. He began his work here as illustrator in the surgical service of the hospital in the fall of 1898, and soon demonstrated that his ability was equal to his task. His faithful water color paintings of tumors of the breast and similar drawings are unique and only paralleled by the best French pictures of pathological subjects. In 1901, Horn became a member of Dr. Kelly's staff of artists. His drawings for the "Vermiform Appendix" and "Medical Gynecology" are too well known to require any praise. Later he was engaged jointly by Drs. Kelly and Cullen, for whom he did most of the illustrations of the books "Myomata of the Uterus" and "Adenomyoma of the Uterus." His last work, just begun, was intended to illustrate a book on diseases of the ovary by Dr. Cullen. Many articles in medical journals by Drs. Halstead, Cullen, MacCallum, Hunner, Watts, Holden and others were

illustrated by Mr. Horn, all with great zeal, fidelity and feeling for the artistic possibilities of a supposedly dry subject. To him all things in nature were capable of displaying beauty; he felt its presence, hunted for it, and brought it out in all his drawings with unerring instinct.

Horn's best work was done in the realistic style. There he was a master. In other respects, however, he may have had some deficiencies. He never liked to make diagrams or work out a problem; he also could not draw a picture intended to represent the salient features of a case or of a group of cases. He could not visualize nor generalize, perhaps because his knowledge of medicine as a science was small. He was not a student and his storehouse of anatomical information was limited. Therefore he rarely had a clear mental picture before he began his diagram. He then began to experiment, alter, and usually ended up with a mediocre picture and his spirit downcast. But if given the opportunity of sketching an operation or of drawing a specimen at his leisure, he was in his element: his eye and hand worked together with splendid precision. He knew how to find the inherent beauty of a line or contour, how to illuminate an object so as to produce a perfect symphony of tints and gradations of tones, which fused together so harmoniously that even the dullest object became interesting if pictured by him. With it all he was ever true and faithful in his interpretation of form so that also in regard to scientific accuracy his medical drawings bear close scrutiny. This is a splendid combination and American medical literature is fortunate to have had an artist of Horn's type contribute to its pages.

AUGUST HORN.

Horn's success is, I think, capable of some analysis. His art training was almost identical with that of a number of the best medical illustrators of to-day, viz., Heroux, Unger, the two Keilitz, Kirchner, Becker and others. They were all Leipzig men, brought up in an art school, where drawing and painting were supplemented by splendid training in the graphic arts (lithography, wood engraving, etching, engraving on copper, etc.). In this manner there was acquired, besides a solid draughtsmanship equal to that of many well-known painters, a perfect technique requisite to representations of minute and exact conditions as demanded in medical work. When they chose medical work as their profession they realized that they had to begin to study once more, for while their artistic skill was perhaps equal to the task of a portrait, a landscape, or a composition, they knew little of medicine. The study of medicine from the standpoint of the medical illustrator was tedious work, there being no instructor to guide them. Each was his own teacher and each developed his own style in conception and execution. All of them have achieved a notable success, a success which, though reached in various ways, had, underlying it, a common training which laid stress on accuracy and technical efficiency. I am convinced that this technical efficiency was greatly aided by practise in the graphic arts, by the painstaking attention to detail learned, for instance, in the work of engraving. I mention this again only because it appears that the medical illustrators of the future could with the greatest advantage be recruited from the ranks of art students, who have had a similar training. Certain it is that technical efficiency is demanded more and more in the medical illustrations of to-day. Twenty years ago the original of a medical drawing was often sketchy in character, even careless in technique. The artist usually depended on the wood engraver, lithographer, or etcher to redraw his original and, in doing so, to give it the exquisite finish which we admire so much in the medical works of a generation ago. To-day the cheaper photomechanic processes have supplanted the engraver and the illustration once made is final. The process, however, is sure to bring out all the technical shortcomings of the original with faithful regularity even accentuating their ugliness and it is apparent that a greater technical skill than ever before is demanded of the artist.

August Horn was 41 years of age when he died. The last twelve years of his life, his best years, were given to medicine. He was a serious minded man and his sincere manner and conscientious attitude toward his fellowmen made him much beloved by all who came in contact with him. He had few outside interests, for his whole soul was centered in his work. His untimely death is indeed a serious loss to the art of medical illustration, since a large part of the work done in this line displays the immature efforts of men or women, who have not had the necessary training for such difficult drawing.

Max Brödel.

NOTES AND NEWS.

At the recent meeting of the Congress of American Physicians and Surgeons held in Washington in May, 1910, a joint session of the American Orthopedic and American Pediatric Societies was held and the subject of epidemic poliomyelitis was discussed. The following resolution was adopted:

"It having been shown by recent epidemics and investigations connected with the same that epidemic infantile spinal paralysis is an infectious communicable disease that has a mortality of from 5 to 20 per cent, and that 75 per cent, or more of the patients surviving are permanently crippled, State boards of health and other health authorities are urged to adopt the same or similar measures as are already adopted and enforced in Massachusetts for ascertaining the modes of origin and manner of distribution of the disease with a view of controlling and limiting the spread of so serious an affection."

A committee with Dr. Robert W. Lovett, president, Boston, Mass., Dr. Irving M. Snow, secretary, Buffalo, N. Y., was appointed to urge the various State and municipal health authorities to take up the work of investigation of the various foci of epidemic poliomyelitis, to study its epidemiology and to instruct the public that the disease is at least mildly communicable.

PERSONAL.

Dr. Frank C. Beall is Professor of Anatomy, Fort Worth University, Forth Worth, Texas.

Dr. John M. Berry is Radiographer and Orthopedic Surgeon, Albany Hospital. His address is 2 Chestnut Street, Albany, N. Y.

Dr. E. Bates Block is Professor of Nervous and Mental Diseases in the Atlanta College of Physicians and Surgeons, and its Visiting Physician to the Piedmont Sanitarium, St. Joseph's Infirmary and the Presbyterian Hospital.

Dr. George Blumer is Dean of the Yale Medical School, Physician to the New Haven Hospital and the New Haven Dispensary, President of the Connecticut Society of Mental Hygiene and Chairman of the Section of Medicine, American Medical Association.

Dr. J. R. B. Branch is Resident Physician and Superintendent, The Macon Hospital, Macon, Ga.

Dr. John R. Caulk is one of the Genito-Urinary Surgeons on the staff at the Washington University, St. Louis. His address is Humboldt Building, St. Louis, Mo.

Dr. R. L. Cunningham is Instructor in Clinical Medicine, Los Angeles Medical Department, University of California.

Dr. C. F. Davidson is Pathologist to the Seattle City Hospital, City Physician and has charge of the Dispensary of the City Hospital. His address is Empire Building, Seattle, Wash.

Dr. Ernest C. Dickson is Assistant Professor of Pathology, Leland Stanford, Jr. University, Fellow of the Rockefeller Institute for Medical Research, and Assistant Pathologist to the Lane Hospital and the City and County Hospital, San Francisco. His address is 2699 California Street, San Francisco, Cal.

Dr. Joseph Erlanger is Professor of Physiology, Washington University Medical School. His address is Forest Park Building. St. Louis, Mo.

Dr. William W. Farr is Physician to the Leamy Home. His address is Chestnut Hill, Philadelphia, Pa.

Dr. Ralph O. Feurbringer is Assistant, Surgical Clinic, University of Marburg, Germany.

Dr. F. C. Goldsborough is Professor of Obstetrics, University of Buffalo, and Attending Gynecologist and Assistant Obstetrician to the Buffalo General Hospital. His address is 459 Franklin Street, Buffalo, N. Y.

Dr. Frederick M. Hanes is Associate in Pathology, College of Physicians and Surgeons, New York. His address is 437 W. 39th Street, New York City.

Dr. August Hoch is Professor of Psychiatry, Cornell University Medical College and Director Psychiatric Institute of the New York State Hospitals.

Dr. Campbell P. Howard is Professor of Theory and Practice of Medicine, State University of Iowa, and Physician to the University Hospital. His address is Iowa City, Iowa.

Dr. Charles R. Kingsley's address is West New Brighton, Staten Island, N. Y.

Dr. J. D. Madison is Attending Physician to the Milwaukee County Hospital and to the Johnson Emergency Hospital, Milwaukee, Wis.

Dr. Harry T. Marshall is Professor of Pathology and Bacteriology at the University of Virginia.

Dr. E. M. Mason's address is Birmingham, Ala.

Dr. Adolf Meyer is Psychiatrist to the Johns Hopkins Hospital. His address is 1035 N. Calvert Street.

Dr. Charles Wilson Mills is Assistant Physician, Loomis Sanatorium, Loomis, N. Y.

Dr. Charles F. Nassau is Assistant Professor of Surgery, Jefferson Medical College, Assistant Surgeon, Jefferson Medical College Hospital, Surgeon to St. Joseph's Hospital and Consulting Surgeon to the Frankford Hospital.

Dr. E. L. Opie is Professor of Pathology, Washington University Medical School, St. Louis, Mo.

Dr. Jewett V. Reed is Assistant Professor of Surgery in the Indiana University School of Medicine, Superintendent of the Indianapolis City Dispensary, Secretary of the Executive Board of the Indiana University School of Medicine, and Visiting Surgeon at the City Hospital.

Dr. E. H. Richardson's address is 216 E. Preston Street.

Dr. Stephen Rushmore is Instructor in Clinical Gynecology, Tufts College Medical School, Visiting Gynecologist, Carney Hospital and Assistant Visiting Physician to the Obstetrical Department, Mt. Sinai Hospital, Boston, Mass.

Dr. Glanville Y. Rusk is Assistant Professor of Pathology, University of California. His address is Berkeley, Cal.

Dr. W. W. Russell is Gynecologist at the Union Protestant Infirmary, the Church Home and Infirmary and the Women's Hospital of Maryland.

Dr. William F. Shallenberger is Resident Surgeon to the Women's Hospital of Maryland, Baltimore.

Dr. Charles J. Spratt's address is Reid Corner, 900 Nicollet Avenue, Minneapolis. Minn.

Dr. Roland L. Stacy's address is Ogdensburg, N. Y.

Dr. A. Raymond Stevens is Adjunct Assistant Attending Genito-Urinary Surgeon to Bellevue Hospital. His address is 40 East 41st Street, New York City.

Dr. Harvey B. Stone's address is 213 E. Preston Street, Baltimore, Md.

Dr. Henry C. Thacher is Assistant in Medicine at the College of Physicians and Surgeons, New York. His address is 20 West 50th Street, New York City.

Dr. Louis W. Warfield is Assistant Professor of Medicine, Wisconsin College of Physicians and Surgeons, and Assistant Superintendent and Resident Physician, Milwaukee County Hospital. Address: Wauwatosa, Wis.

Dr. Percy T. Watson's address is Fenchow, Shansi, China, where he is stationed as a medical missionary.

Dr. Harry I. Wiel is Assistant in Medicine in Charge of Tuberculosis Class, San Francisco Polyclinic.

Dr. Otis B. Wight is Lecturer in Gynecology, University of Oregon, and Clinical Assistant in Surgery, Free Dispensary, Portland, Oregon.

Dr. J. Whitridge Williams is Honorary President of the Glasgow Obstetrical Society.

Dr. Paul G. Woolley is Professor of Pathology, University of Cincinnati College of Medicine, Dean of the Medical Faculty and Director of the Laboratories of the Cincinnati Hospital.

NOTES ON NEW BOOKS.

Diseases of the Heart and Aorta. By A. D. Hirschfelder, M. D. 632 pages. (*J. B. Lippincott Company, 1910.*)

The past few years have witnessed an unusual activity in the clinical study of abnormal cardiac conditions. Instruments of precision such as the sphygmomanometer, the polygraph, the electrocardiograph, and the orthodiagraph have furnished data that have added much to our knowledge and have corrected or confirmed opinions that were otherwise impossible of scientific demonstration. This new knowledge has rendered obsolete many of the older text-books. It is a pleasure, therefore, to find in Dr. Hirschfelder's book a careful and critical review of this new material and an attempt to combine it with the older cardiac pathology. In addition to this the relation of clinical conditions to those which are observed in the physiologic laboratory is discussed by one whose original researches on the pathologic physiology of the heart makes his opinion of unusual interest.

The first third of the book deals with the general principles of cardiac physiology, pathology, methods of examination, and therapeutic measures. The conventional anatomic introduction is replaced by a physiologic introduction and throughout this part of the book the physiologic point of view is evident; noticeably in the discussion of the arterial and venous pulses, the effect of exercise, and the action of drugs. The latter two-thirds of the book deals with the various diseases of the heart. The division of diseases is made on the anatomic basis so far as possible. Interesting chapters are introduced on vasomotor crises and angioneurotic lesions, on angina pectoris, on the heart in pregnancy and labor, on heart-block and the Adams-Stokes syndrome, on paroxysmal tachycardia, and on the heart in disturbances of the thyroid. It is to be regretted that the author has not given separate consideration to the common and important changes associated with continuous high blood pressure, with its distinct clinical picture and special dangers. The chapter on the so-called cardiac neuroses is short and indicates the unsatisfactory character of our knowledge of these conditions.

The book is illustrated with numerous photographs, X-ray pictures, drawings, and illustrative case histories. The majority of these are original and highly valuable in rendering more easy an understanding of the subject matter. Each chapter is followed by a full bibliography which adds greatly to its reference value.

On the whole, the book may be regarded as the best that we have in English on this subject. The discussions are often of a theoretical character, too technical perhaps for a general practitioner, but to one who has followed the many recent advances in our knowledge of diseases of the heart, they are instructive and stimulating.

A. W. H.

Fiske Fund Prize Dissertation, No. LIII. The Classification and Treatment of Diseases Commonly Known as Rheumatism. By Frank E. Peckham, M. D. (*Providence: Snow and Farnham Company, 1910.*)

We welcome anything which throws light on the obscure problems of arthritis, but it cannot in honesty be said that this work lessens the darkness. The conditions "known as rheumatism" are classified by the writer as "villous arthritis, atrophic arthritis, hypertrophic arthritis, infectious arthritis and gout." The writer opens with the statement that "A classification must be founded on some logical basis, ..." with which we all agree. But should villous arthritis then be regarded as a special form? Is it not a change which occurs with various joint disturbances and which has in no respect a specific character? For example villous arthritis may occur with traumatic arthritis, with tuberculous arthritis or with what is termed arthritis deformans. Then again when one form is classified on an etiological basis, e. g., infectious arthritis and another on an anatomical basis, e. g., hypertrophic arthritis, can we be regarded as proceeding on a logical basis? The objection is also made stronger by the fact that there is good proof that many of the cases of hypertrophic arthritis are secondary to an infection. The term infectious arthritis—would not *infective* arthritis be a better designation—is used to-day in a very loose way. It would be wiser if we restricted it to those forms of arthritis in which the bacterial origin is definitely proved; as for example, tuberculous or gonorrhœal arthritis.

Much of the treatment advised for these conditions is to be commended, particularly the emphasis which is placed on the uselessness of calling many forms of arthritis rheumatism and directing treatment, especially by drugs of the salicylate class, to that supposed disorder. There are not many who will agree with the author as to the results to be expected from electrical treatment. The man who believes enthusiastically in this is to be envied; the influence of his belief is probably more important that the electricity itself.

Golden Rules of Refraction. By Ernest E. Maddox, M. D., F. R. C. S. Ed. "Golden Rule" Series, No. XII. Third Edition. Revised. Price 1s. (*Bristol: John Wright and Sons, Ltd.*)

What was said of this work in this journal in May, 1903, holds true of it to-day. In very small compass it holds much useful information for students beginning the study of refraction, but we cannot recommend such condensed food as a nutritious diet.

Messrs. Lea & Febiger (Philadelphia and New York) have issued a convenient pocket-sized Practitioners' Visiting-List for 1911. In the diary there is space for recording visits to thirty patients per week. For quick reference there are numerous tables which are useful to the practitioner in his daily work, and also rules for aid in surgical and medical emergencies. It is neatly printed and bound. Price $1.25.

Chronicles of Pharmacy. By A. C. Wootton. Two vols. (*London: Macmillan & Co., 1910.*)

A study of the "chronicles of pharmacy" is likely to lead one into many interesting by-paths and side excursions. Pharmacy, as we know it to-day, can hardly be regarded as other than a prosaic matter, but in its long history it has come through many varied experiences. As the author of this work well states it has been associated "with magic, with theology, with alchemy,

with crimes and conscious fraud, with the strangest fancies, and dogmas and delusions, and with the severest science." The list of those who have contributed to pharmacy is a long one. From Apollo and Chiron the Centaur to Thomas Dover the Buccaneer, we have all sorts and conditions of men.

This work has evidently been a labor of love and bears the marks of having been in preparation for many years. It would be difficult to write such a work in any brief time for the great variety of information must have been obtained from many sources and demanded long and patient search. A pathetic feature was the death of the author while the work was going through the press. In the preface he asks for corrections, which he adds, with prophetic voice, he may not have the opportunity of utilizing.

There is so much of interest in the volumes that it is not easy to choose what should be specially noticed. In the discussion of pharmacy in early times, the myths of the ancients, pharmacy among the Pharaohs, in the Bible, and of the Arabians are dealt with. Of the remedies in use at the time of Hippocrates it is worthy of note that among a list of one hundred and ninety-five drugs, thirty-four are still in use in ordinary medicine and some others are domestic remedies. There is an interesting chapter on the Arabian school of medicine and pharmacy, especially in regard to its influence on European knowledge.

The account of pharmacy in Great Britain has many interesting points and of course describes the great battle over the dispensaries between the physicians and apothecaries. One does not wonder at the protest against the apothecaries when some of the amounts charged for medicines in those days are quoted. The chapters on Magic and Medicine, and Dogmas and Delusions are full of interesting matter and perhaps none is more so than the account of the so-called sympathetic remedies. The most often quoted example is Sir Kenelm Digby's "power of sympathy," but he did not originate the idea. Pliny had the germ of it when he advised that if one should be sorry for a blow given, if he spit into the middle of his hand, "the party that was smitten shall presently be free from pain." Paracelsus was a strong advocate of the value of a sympathetic ointment which was to be applied to the weapon which had given the wound, but he threw out an anchor by saying that it was not of value if an artery was severed or the brain, heart or liver was injured. Robert Fludd, the Rosicrucian, was a warm advocate of the sympathetic ointment, and Madame de Sévigné was another firm believer in this principle of treatment. It is, however, with the name of Digby, that the fame of the power of sympathy is especially associated. The chapters on Masters in Pharmacy and Royal and Noble Pharmacists contain references to many interesting characters and their contributions to pharmacy. Sir Walter Raleigh's Cordial and Bishop Berkeley's Tar Water receive due mention. Under the contributions from chemistry comes the history of many of our modern agents. Many details are given in reference to the discovery of the action of the metals which form so important a part of our materia medica to-day.

The second volume has perhaps even more varied discussions. The use of animals or parts of them in pharmacy makes rather depressing reading, sometimes also amusing. A cure for drunkenness has certainly something to recommend it: "Eels being put into wine or beer and suffered to die in it; he that drinks it will never endure that sort of liquor again." The chapters on some Noted Drugs, Familiar Medicines and Noted Nostrums are full of interesting points. We are to-day returning to the use of ipecacuanha as a remedy for dysentery. This was the disease for which it was employed when introduced into Europe from Brazil by a Portuguese friar in 1625. It was brought specially to notice by Helvetius who cured the son of Louis XIV of dysentery by its use. Many old favorites are discussed, "Dover's powder," "Gregory's powder," "Plummer's pills," "Friar's Balsam," etc. Chapters on Persons in History, Pharmacy in the Nineteenth Century, and Names and Symbols conclude the work.

We can very heartily recommend these volumes to all who are interested in the history of medicine, but it is difficult to imagine that anyone could fail to find something which would repay the reading of them. It is to be regretted that the author did not live to see his work published. He has given us an excellent addition to the historical part of our libraries.

Rational Hydrotherapy. A Manual of the Physiological and Therapeutic Effects of Hydriatic Procedures and the Technique of Their Application in the Treatment of Disease. By J. H. KELLOGG, M. D., etc. Illustrated. Fourth Revised Edition. (*Philadelphia: F. A. Davis Company, Publishers, 1910.*)

Those who desire a large treatise on hydrotherapy will do well to purchase this volume, for they will find the subject treated lucidly and in great detail. The author in his preface states that "while water is recognized as without doubt one of the most valuable of all natural agencies, the writer has never permitted himself to be classed with those enthusiasts who place their trust in it as an exclusive measure. It is best employed in connection with the use of electricity, massage, and medical gymnastics. Rational diet is as essential in the treatment of the majority of cases of acute and chronic disease as is water. In the treatment of chronic disorders the regulation of exercise, dress, and of other habits of life is also a matter of paramount importance; also the disuse of tea, coffee, tobacco, and alcoholic beverages, which are often found to sustain a very direct causative relation to the patients' maladies, and are without doubt responsible for many failures in which the fault has been unjustly charged to the inefficiency of water as a therapeutic agent." This work, of over 1200 pages, is divided into 4 parts. Part I contains 6 chapters: Historical; The Physics of Water, Air, Heat and Light in Relation to Hydrotherapy; Anatomy and Physiology in Relation to Hydrotherapy; The Physiological Effects of External and Internal Applications of Water; the Physiological Effects of Friction or Mechanical Irritation of the Skin; and The Physiological Effects of Light. Part II is in 4 chapters: The General Principles of Hydriatics; The Therapeutic Effects of Hydriatic Applications; General Rules, Principles and Suggestions Relating to the Practical Employment of Hydrotherapy; Hydriatic Institutions and Their Equipment, and the General Management of Cases. Part III has but 1 chapter: The Technique of Hydrotherapy, and Part IV has 4: Hydriatic Prescription Making; Summary of Experimental Work; Hydriatic Measures for Regulating Blood Pressure; and Recent Advances in Hydrotherapy. There is also a very full bibliography and index. After a careful study of this work any doctor should have an intelligent knowledge of the value, uses, and methods of hydrotherapy.

The Surgery of Childhood, Including Orthopædic Surgery. By DEFOREST WILLARD, M. D., Professor of Orthopædic Surgery, University of Pennsylvania. With 712 illustrations, including 17 in colors. Price $7. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

The volume is dedicated to the late D. Hayes Agnew, M. D., LL. D. The author says that one of the principal objects of the book is to induce the earlier examination and recognition of the surgical diseases of childhood, since irreparable damage frequently follows through delay in investigation or treatment by the attending physician or surgeon. The importance of the clinical examination of each patient is emphasized, but in addition he urges the systematic use of accurate and scientific methods of investigation by instruments of precision. He has endeavored to select and present methods of diagnosis and treatment that in his long experience have proved to be of practical service.

The book is divided into thirty chapters, as follows: I, General Surgical Considerations; II, Surgery of the Head and Face; III, Surgery of the Neck and Chest; IV, Surgery of the Abdomen; V, Surgery of the Genito-Urinary Organs; VI, Burns, Frost-Bites, Boils; VII, Orthopædic Surgery; VIII, Fixation Dressings and Splints; IX, Rotary Lateral Curvature of the Spine; X, Constitutional Diseases Productive of Deformities; XI, Fractures in Children; XII, Tuberculosis of Bones and Joints; XIII, Spinal Caries, Tuberculous; XIV, Spine, Various Surgical Conditions; XV, Pelvis; XVI, Hip-Joint Disease, Tuberculous; XVII, Hip, Various Surgical Conditions; XVIII, Knee-Joint, Tuberculosis; XIX, Knee, Various Surgical Conditions; XX, Ankle and Foot Injuries; XXI, Surgical Conditions of the Shoulder; XXII, Surgical Conditions of the Elbow-Joint; XXIII, Surgical Conditions of the Wrist and Hand; XXIV, Non-Tuberculous Diseases of the Joints; XXV, Non-Tuberculous Bone Diseases; XXVI, Paralysis; XXVII, Talipes; XXVIII, Various Deformities of the Feet; XXIX, Congenital Malformations and Dislocations; XXX, Congenital Deficiencies of Bones.

It is interesting to note that the author advocates nitrous oxide as the ideal anesthetic for short operations on children. This is somewhat at variance with the reports of other authors.

He emphasizes the great importance of economizing the body heat in children by wrapping all portions of the body, outside of the operative area, in cotton covered with wax paper; by the use of electrically heated or hot water operating pads, and by non-exposure of surface before, during and after operation.

There are many references throughout the book, a number of them being from the author's writings, and in addition at the end of the book there is a bibliographical appendix of four pages containing a complete list of his numerous publications.

The illustrations are plentiful and for the most part good, although some, especially those showing instruments, are too small to be of any use.

The book is well written and will be especially interesting to those who have had the privilege of attending Dr. Willard's clinics, and will serve as a very useful and practical reminder of this distinguished surgeon. J. S. D.

A System of Syphilis in Six Volumes. Edited by D'Arcy Power, M. B. Oxon., F. R. C. S., and J. Keogh Murphy, M. C. Cantab., F. R. C. S. With an introduction by Sir Jonathan Hutchinson, F. R. S. Vols. V and VI. Price of each $13.50. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

The fifth volume contains paper on "The Affections of the Skin in Syphilis," "Ocular Syphilis," "Naval Syphilis," and "Syphilis in the Upper-Air Passages," and the sixth volume completes this system with a series of papers devoted to a history of this disease "in the more important armies," to various aspects of syphilis in the navy of the United States of America, and the Royal Navy. To this volume also there is prefixed a brief introduction by one of the editors, Dr. Murphy, and the last paper in it is one on "The Value of Justus' Test in the Diagnosis of Syphilis." In both these volumes there are numerous excellent photographs and colored plates. Taken as a whole, it is the most complete System of Syphilis in the English language, and an excellent one. Were it not for the price of the individual volumes it would have a larger sale. The last volume, with a large amount of statistics bearing on this disease as it has appeared in different armies and navies at varying epochs and in many localities is a most interesting one to public health officers and sanitarians, as well as physicians. In the Editors' Afterword occur these sentences which will define the character of the work: "Attention has been called by some of our critics to the amount of repetition in the work when considered as a whole. This appeared to the Editors to be unavoidable, as it was necessary to make each volume as far as possible complete in itself; moreover each article represents the individual and mature judgment of its author, which has sometimes differed from that of other eminent authorities whose conclusions had already been given." Such frankness disarms the critic. He may not agree with the individual writer on many points, but he must not forget that the author is a man of large experience expressing his mature judgment. On "Syphilis," there is probably more disagreement among physicians than on any other disease, due to its proteid form, and great local and individual differences in its severity. If Ehrlich's "606" proves as valuable as is now hoped it will, much of the treatment advocated in this volume will be antiquated in a few years, but the System will still remain a notable one, most valuable to all syphilographers.

A Treatise on Diseases of the Eye. By John Elmer Weeks, M. D., etc. Illustrated (*New York and Philadelphia: Lea & Febiger, 1910.*)

This is a thoroughly satisfactory text-book on the Diseases of the Eye. Throughout it shows that the author has very carefully planned a text-book based on his own personal experience and knowledge, without using any existing text-book as a model. The author has been thoroughly alive to the fact that there have been many valuable and important contributions to ophthalmological literature in recent years, and he has judiciously incorporated this material into the text—the result being a new and thoroughly modern text-book, showing a forceful individuality.

All pathological and bacteriological matter pertaining to Eye Diseases has been most fully and carefully considered, and in such a manner as to show that the author is not only an ophthalmologist, but a real pathologist as well.

We commend this book to all students. We believe that Weeks has produced the best American text-book on the eye written up to the present time—a book which is in the same class as the German "Fuchs," which is equivalent to saying, without further commendation, that it is an extraordinarily excellent text-book on Eye Diseases. B. B. Browne, Jr.

Refraction and Motility of the Eye. With Chapters of Color Blindness and the Field of Vision. Designed for Students and Practitioners. By Ellice M. Alger, M. D., etc. Illustrated. Price $1.50. (*Philadelphia: F. A. Davis Company, 1910.*)

This book was a distinct disappointment to the reviewer. A modern text-book setting forth the methods and practices of the present-day oculist used in correcting the refraction-errors of the eye would be a welcome addition to the many very excellent text-books on the Diseases of the Eye which we have. This book, in the main, only states the familiar optical laws found in most text-books. A considerable amount of irrelevant subject matter helps to increase the size of the volume, while much material, which ought to be found in its pages is either omitted or dismissed in a few words. Sufficient attention is not given to the various astigmatic tests, nor to the make up of trial cards, their illumination, etc. The book contains many devitalized facts, in the main correctly stated, but it would not be possible to acquire valuable and comprehensive knowledge of practical refraction from its pages, and we do not believe that it satisfactorily meets the needs of any class of readers.

B. B. Browne, Jr.

Pathogenic Micro-Organisms, Including Bacteria and Protozoa. By William Hallock Park, M. D., and Anna W. Williams, M. D. Fourth edition, enlarged and thoroughly revised. (*Philadelphia: Lea and Febiger, 1910.*)

We have previously had the opportunity of calling attention to the excellent text-book on Pathogenic Bacteria and Protozoa by Park and Williams. The present edition deserves no less praise

than former editions and like its predecessors can be especially recommended to physicians who are interested in public health work.

The methods of bacteriological diagnosis employed at the Research Laboratory of the Board of Health of New York City form the basis of the book, although the methods employed in other laboratories are by no means neglected. The chapters on Tuberculosis, Diphtheria, and Typhoid Fever are especially to be praised since they include not only excellent descriptions of the cultural characteristics of the organisms concerned in these infections, but also many of the investigations in the field of Immunity and Serum Therapy, which have resulted from the bacteriological study of these diseases. The other pathogenic bacteria are well described and the methods for the isolation of the various microörganisms concerned in Human Pathology are clearly and accurately given. There are, however, certain features of the book which, from the standpoint of the teaching bacteriologists, are to be criticized.

For the average student it seems as if too much attention has been devoted to certain organisms and too little space given to the description of other no less important pathogenic bacteria. Thus the chapters on Tuberculosis and on Diphtheria occupy nearly 40 pages each, and that on the Typhoid Bacillus, nearly 30 pages, while the description of the Gonococcus and its characteristics is limited to 7 pages, that of the Meningococcus to a little more, and the Plague Bacillus receives an inadequate description confined to 4 pages. For the student of Bacteriology these latter organisms are quite as important as the former.

Again the methods in which organisms are grouped are also open to much criticism, and it is difficult to see exactly the reason why certain bacteria are included in the same chapters. Thus the Micrococcus of Malta Fever and the Micrococcus Zymogenes of MacCallum and Hastings are placed in the chapter with the Gonococcus, and the Bacillus of Soft Chancre, an arrangement for which there is no justification, either from the cultural characteristics of the organisms, or from their pathogenic action. The Anthrax Bacillus is grouped with the pathogenic anærobes, and the essential differences in the methods which must be employed in the cultivation of these various organisms are not clearly brought out. The attempt has also been made to classify certain organisms derived mainly from the intestinal tract according to their cultural characters, regardless of certain well-marked morphological distinctions and a hopeless mix-up has resulted. The encapsulated bacteria which form a distinct group of microörganisms are placed with *Bacillus coli*, *Bacillus typhosus*, and *Bacillus para-typhosus*, and with them is included the microörganism of swine plague with entirely different cultural characteristics. This latter organism indeed should be the type organism for the hemorrhagic septicæmia group in which the author places several infections of man, although the resemblance of these diseases and the microörganisms thus far encountered in them to the condition of hemorrhagic septicæmia in lower animals is by no means clearly marked.

No attempt is made to apply correct botanical names to the various bacterial species, an unfortunate omission for the student since bacteria come strictly under the rules of botanical nomenclature, and when these rules are properly applied with the name of the author first correctly designating the organism, many of the historical facts of bacteriology are impressed upon the mind.

Finally there are a number of investigations of the first rank by American bacteriologists which have received scant attention. The work of Jordan and Harris on Milk Sickness is not included, and the investigations of Dorset, Bolton and McBride on the etiology of Hog Cholera are not mentioned. The last-named investigation has now been repeated in many of the bacteriological laboratories abroad, the results of these men have been abundantly confirmed and this piece of work stands out as one of the finest achievements that has ever been made by bacteriologists in this country.

The book in our estimation contains a large amount of very valuable information, and can be especially recommended to the practicing bacteriologist. The faults which we have mentioned are but minor points of arrangement and detract but little from the great value of the work.

The section of the book devoted to Protozoölogy, written separately by Dr. Williams, leaves nothing to be desired in the way of concise, clear description of the protozoa, and like the Bacteriology proper is especially to be praised for the diagnostic methods which it emphasizes.

Report on the Measures Taken Against Malaria in the Lahore (Mian Mir) Cantonment. By The Honorable Mr. R. Nathan, C. I. C., I. C. S.; Lieutenant-Colonel H. B. Thornhill, C. I. C., I. A.; and Major L. Rogers, M. D., F. R. C. P., F. R. C. S., I. M. S. 1909. (*Calcutta, India: Superintendent Government Printing, 1910.*)

This report is divided into the seven following parts: 1, Preliminary; 2, Description of Lahore Cantonment; 3, First Series of Experimental Operations in Lahore Cantonment; 4, General Anti-Malarial Operations in the Cantonment; 5, Result of General Anti-Malarial Measures; 6, Summary of Conclusions; and 7, Applicability to India of Measures Adopted in Other Parts of the World. To all interested in the problem of the extermination of malaria this is a most valuable report, for in spite of the best efforts of the military officers and physicians, and of admirable work done, it has not been possible to reduce the prevalence of this disease in the Lahore Cantonment. In fact the results are very similar to those that have followed the introduction of the water filtration in Washington, D. C., where though the plant to this end is as good as can be, the diminution in the amount of typhoid fever has not followed as was expected. It merely shows that in all these problems there are many factors which have yet to be carefully studied and worked out.

Naval Hygiene. By James Duncan Gatewood, M. D. Instructor in Naval Hygiene, U. S. Naval Medical School, Washington. Medical Inspector, U. S. Navy. Illustrated. Price $6. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

This book on Naval Hygiene, by Dr. Gatewood, is written especially from the standpoint of a medical man occupied with the problems of naval hygiene, and is designed primarily for the students interested in this field of medicine. It cannot be looked upon as a mere record of scientific facts, although a scientific basis for the practical work outlined in this book is clearly indicated.

The book is divided into eight chapters. The first chapter deals with naval vital statistics, and in it the author dwells at length upon the various forms of disease met with in tropical and temperate climates and attempts to show the varied susceptibility or immunity which the enlisted men exhibit towards these diseases. The tables giving the sick rates, death rates, etc., are well arranged and are of great value in the interpretation of vital statistics.

In the second chapter the problem of the ventilation of ships is taken up, and emphasis is laid upon the necessity for a proper ventilation of all the different parts of the vessel. The various methods employed to rid vessels of obnoxious odors and gases are enumerated and the clear distinction between the theoretical ideas of the trained laboratory man concerning ventilation and the practical difficulties encountered on ship board in carrying out these ideas is clearly indicated. In our opinion this chapter is the most interesting and the best written of all the chapters of the book.

The third chapter deals with the problems of light and em-

phasizes the effect of well-lighted quarters upon the physical and mental health of the enlisted men, and in this chapter the author maintains that gloomy surroundings have a far greater influence upon the health of the men than is generally supposed.

The other chapters of the book deal with such problems as water supplies, drainage, food, clothing and disinfection. In the chapters dealing with disinfection the various methods employed on board ship are given, and the numerous duties of the officers at the recruiting stations are described. The importance of a more stringent examination of the applicants for enlistment at the recruiting stations is indicated, and Dr. Gatewood is inclined to put the responsibility of much of the high sick rate on board ship upon the recruiting officer, believing that many individuals are permitted to enlist, even though they are physically unfit to withstand the routine of ship life.

The book is well written and will, we believe, prove of great value to the student of naval hygiene bringing together most of the important facts and principles to be known in this field. Had the author condensed his material into a smaller volume he would have added greatly to the value of his publication.

Osteology and Syndesmology. By Howard A. Sutton, M. D., etc., and Cecil K. Druker, B. S. Price $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

The authors endeavor in this work to present these two subjects in a way to make them more easily learned than they can be in the usual anatomical text-books. "The bones follow one another in the order found simplest and most useful in presenting the course in osteology at the University of Pennsylvania. Summaries occur at the end of every section, which is not a summary in itself. It is hoped they will facilitate review and will be of service in the quizzing of the student with his fellows—a method of work most necessary in such a course. Each joint is discussed after the bones which compose it, instead of in a separate division at the end of the book." These quotations from the preface show the arrangement and purport of the book—a form of quiz compend. Such a work finds a welcome place on the book-shelf of many a student, but it cannot take the place of a more scientific anatomy.

Hernia: Its Cause and Treatment. By R. W. Murray, F. R. C. S., etc., Illustrated. Second Edition. Price 6s. (*London: J. & A. Churchill, 1910.*)

This brief treatise on hernia is merely an exposition of the author's views and practice on the subject—it does not pretend to be more than this. The author believes that inguinal hernia, in the large majority of cases, is due to a sac of congenital origin, which is entirely separate from that which involves the tunica vaginalis, and that this "Saccular Theory" is applicable to all forms of hernia. He has had as good success with his operation as many other surgeons have had with theirs, and it must be left to those interested in hernia to read the book carefully and decide on the relative merits of the operation.

The Hand-Book of Electro-Therapeutics. By William James Dugan, M. D. With ninety-one illustrations. (*Philadelphia: F. A. Davis & Co., 1910.*)

This is a work which deserves special attention from physicians interested in this branch of medicine. It will also richly repay careful study by the general practitioner who, knowing nothing about electricity, ignores its great usefulness in the treatment of a variety of disorders, some of which are very intractable to other means of treatment—for example neuritis.

The book is written in a clear and concise fashion. The different kinds of electric currents and their uses are described at sufficient length for a work which deals with so extensive a subject in so small a compass. A large variety of useful apparatus is amply illustrated.

That treatment by electricity has been greatly abused by the unscrupulous and by those who had little knowledge of physiological or pathological conditions, there can be no doubt.

For instance the author speaks of the extensive use made of the high frequency current in the treatment of hysteria; he points out that it is irrational to use a current which lowers blood pressure in a disease where blood pressure is already below normal, instead of using the static current which would tend to reestablish normal arterial tension, without sacrificing any of the psychic effect.

In the treatment of goitres, carcinoma, enlarged prostate and other surgical diseases, the author very properly specifies that electricity should not be used unless a radical operation is for some reason contraindicated, or as an auxiliary after operation to build up the general health of the patient. The chapters on Magnetism, Heat and Light, and Death by Electricity were to the reviewer, particularly interesting and instructive.

By way of criticism the reviewer has nothing to say unless it be to the publisher for the mistake in Fig. 70, between pages 126 and 127, where an "X-ray" plate of an ankle (anterior view) is called a wrist.

The book, taken as a whole, is a very strong plea for the more extended use of electrotherapeutics by members of the profession who, being satisfied that this important agent rests on a firm scientific basis, will use it as such, and not as a mere vehicle for suggestion.

John Sebastien Derr.

Practical Physiological Chemistry. A Book Designed for Use in Courses in Practical Physiological Chemistry in Schools of Medicine and of Science. By Philip B. Hawk, M. D., Ph. D., etc. Third Edition. Revised and Enlarged. Illustrated. Price $2.50. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

That this book has met with approval is seen by the fact that this edition has followed the second within a year. In its present form certain corrections have been made and "a number of qualitative tests and qualitative methods," that are new, have been added. The work was favorably commented upon in this Journal, December, 1909.

A Treatise on Orthopedic Surgery. By Royal Whitman, M. D. Fourth Edition. Revised and enlarged. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1910.*)

The author states in his preface that "this edition has been thoroughly revised. New material and new illustrations have been added, and in its present form it is believed that the book fairly represents this department of medicine at date of issue." The importance of the illustrations was drawn attention to in the review of this book which appeared in the Bulletin in August, 1907. Its value as a treatise on Orthopædics was noted, and in its present form this work is a most excellent one, and especially serviceable to students from the clearness with which matters are presented, and the authority given it by the author whose work in orthopædics is recognized as preeminent in this country.

Normal Histology with Special Reference to the Structures of the Human Body. By George A. Piersol, M. D., Sc. D., Professor of Anatomy in the University of Pennsylvania. 438 illustrations many of which are in colors. Eighth Edition (rewritten). Price $3.50. (*Philadelphia and London: J. B. Lippincott Company.*)

The author's aim has been, to quote from the preface, "to present descriptions which should include the salient features of the various structures with sufficient fullness to impress important details without wearying minutiæ; too great conciseness, on the

one hand, and too great elaboration of detail, on the other, are alike unsatisfactory."

A satisfactory middle ground has been reached in the clear and concise presentation of the essential features of the various organs and tissues.

The book is adequately illustrated, the excellent figures bearing out the author's statement that the preparations, from which they were drawn, were selected to show the usual rather than the unusual histological appearances.

One feature of the work is the insertion in certain instances of a brief outline of the macroscopic features of an organ before the microscopic appearances are described.

The book will be especially appreciated by students beginning their work in Histology, for whom indeed it is primarily intended.

A Manual of Physiology With Practical Exercises. By G. N. STEWART, M. A., M. D. Edin., etc., Professor of Experimental Medicine in Western Reserve University, Cleveland. With colored plates and 450 other illustrations. Price $5. Sixth Edition. (*New York: William Wood & Co., 1910.*)

The third edition of this work was reviewed in the BULLETIN in May, 1899. That three more editions have been called for since then shows that its merits to which attention was called have made it a favorite text-book with students. It has grown larger with its years of age, but it has at the same time become a better work, and thus its success is well deserved. It is not an easy book to learn from, but the student who has mastered it will be thoroughly well grounded in the principles of physiology.

Paludism—Being the Transactions for the Study of Malaria in India. Edited by MAJOR S. P. JAMES, M. D., I. M. S. Issued under the authority of the Government of India by the Sanitary Commissioner with the Government of India, Simla. (*Simla: Government Central Branch Press, 1910.*)

This is the first number (July, 1910) of a new journal on Paludism to be issued at "irregular intervals." Special students of malaria will be interested to note its appearance, as there are so many questions still to be solved in regard to this disease, and India is one of the countries which suffers greatly from it, and where the chances to study it are especially good. The famous discoveries by Ross, in relation to the malarial parasite and its propagation, were made in India, and there is little doubt that other valuable information will come from the well-trained English medical officers in that country. This number contains some important "Notes on Mosquitoes," and unquestionably this new journal will be required by all those who wish to be masters of the subject.

The Essentials of Histology. Descriptive and Practical. For the use of Students. By E. A. SCHÄFER, M. D., etc. 8th Edition. Price $3.50. (*Philadelphia and New York: Lea & Febiger, 1910.*)

This edition varies but little from the seventh which was favorably noticed in our columns, December, 1907. In its new form it is a little larger, but this increase in size is due mainly to a greater number of illustrations, many in colors. These make the work a most helpful one to students, and its numerous editions are a proof of its merit.

Pulmonary Tuberculosis and its Complications. By SHERMAN G. BONNEY, A. M., M. D. Second Edition. Price $7 net. (*Philadelphia: W. B. Saunders Company, 1910.*)

The first edition of this book was reviewed in the BULLETIN of June, 1909. Additional material and chapters increase the already voluminous collection of facts. It is to be regretted that data are often cited in such profusion as to leave their bearing on the topic discussed rather indistinct. Not always does the author correlate clearly his large material. In this edition we find the chapter on bacilli resembling the tubercle bacillus, enlarged and admirably improved. In the discussion of the relation between the human and bovine types, Detre's scheme of differential diagnosis is given extended notice without any hint of the serious doubts thrown upon it by various authors. The statement as regards the excessive use of the subcutaneous tuberculin test for diagnosis is to be heartily commended, and deserves wide circulation. But the recommendations as regards the maximum dose to be employed, if the method must be resorted to, are unnecessarily cautious. There is in this chapter, too, an unfortunate confusion in the use of "local" for both "local" and "focal" reaction. In the section on the cutaneous and ophthalmic tests, there is not enough emphasis laid upon the almost utter uselessness for diagnosis in adults of the positive cutaneous reaction, nor is there made clear the importance of observing the percentage strength of the solutions used for the eye tests. That, at present, little help is derived from the Röntgen Ray in early diagnosis, is a justifiable conclusion. The new chapter on the Regulation and Restriction of Travel for Consumptives, shows the growing demands of our social sense. The chapter on Immunity is the least satisfactory. The facts are not well selected, and the discussion not judicious. In spite of the faults cited, the reader will find the book full of most valuable information. S. W.

Hookworm Disease. Etiology, Pathology, Diagnosis, Prognosis, Prophylaxis and Treatment. By GEORGE DOCK, A. M., M. D., Professor of the Theory and Practice of Medicine, Medical Department of Tulane University of Louisiana, New Orleans, and CHARLES C. BASS, M. D., Instructor of Clinical Microscopy and Clinical Medicine, Medical Department of Tulane University of Louisiana, New Orleans. Illustrated with fifty-nine special engravings and colored plates. Price $2.50. (*St. Louis: C. V. Mosly Company, 1910.*)

So much attention has been given to the prevalence of the Hookworm Disease in the South, both by the press at large and the great numbers of articles appearing in the medical journals that we feel sure a treatise on the subject is most opportune.

In a book of 250 pages, Dock and Bass have given an excellent résumé of what is known concerning the Etiology, Pathology, Diagnosis, Prognosis, Prophylaxis and Treatment of this disease. Beginning with a most interesting historical review of the subject we find complete chapters devoted to the geographic distribution and economic importance of the disease, its zoölogic features, pathologic anatomy, and symptomatology; each chapter is replete with illustrations.

To the practicing physician we particularly recommend the chapters devoted to the diagnosis and treatment of the disease. The remarkable results obtained through the use of Thymol makes this drug almost a specific.

While the book has been primarily written for physicians, hygienists, employers of labor, and others interested in sanitation will find valuable information within its covers.

J. S. B.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D., assisted by LEIGHTON F. APPLEMAN, M. D. Vol. III. September, 1910. (*Philadelphia and New York: Lea & Febiger, 1910.*)

The latest and most important papers on "Diseases of the Thorax and its Viscera, including the Heart, Lungs and Blood Vessels," on "Dermatology and Syphilis," on "Obstetrics," and on diseases of the "Nervous System" are reviewed and discussed in this volume. What makes this series valuable is first the selection of the papers out of the immense mass of material constantly appearing; and second, their treatment—their careful grouping, and the broad review of the subject in hand by the

editor of the section. The different departments of medicine are well treated, and the busy practitioner can get much help out of these volumes.

International Clinics. Edited by HENRY W. CATTELL, A. M., M. D. Vol. III. Twentieth Series. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

Out of the many interesting papers in this volume it is difficult to select one as more worthy than the rest of special notice. There are articles on Diagnosis, Treatment, Teeth and Oral Cavity, Gynæcology, Medicine, Surgery, Miscellany, and A Medical Home-Coming Week, and specialists in any of these departments will find noteworthy contributions to their own line of work. These articles do not appear in other journals, so that this series records a very large number of rare clinical histories.

Diseases of Infancy and Childhood; their Dietetic, Hygienic and Medical Treatment. A Text-book designed for Practitioners and Students in Medicine. By LOUIS FISCHER, M. D., Attending Physician to the Willard Parker and Riverside Hospitals, etc. Third Edition. Illustrated. Price $6.50. (*Philadelphia: F. A. Davis Company, Publishers, 1910.*)

A review of the first edition of this book appeared in the BULLETIN two years ago. The issue of the third edition of a work of this magnitude indicates that it has met with gratifying success. In the present issue several new chapters have been added as for example on epidemic cerebro-spinal meningitis and its treatment by the Flexner serum and lumbar puncture, on scabies indicanuria, acetonuria, and diabetes. New illustrations have also been added.

If any criticism of the book as a whole were offered it might justly be said that too much space in it is given to too many subjects. For instance the chapter on the bacteria of the intestines would be equally valuable if the bacteria were described in less detail and the results of more recent investigations had been embodied in it. The same objection might be urged to the account of the bacteriology of diphtheria. This information might have been much abridged without, in any manner, lessening the value of the chapter which is perhaps the strongest in the whole book. These, however, after all are minor defects and the present edition is a valuable manual for the guidance of practitioners who are treating the diseases of infancy and childhood.

A Manual of Hygiene and Sanitation. By SENECA EGBERT, A. M., M. D., etc. Fifth Edition. Enlarged and thoroughly revised. Illustrated. Price $2.25. (*Philadelphia and New York: Lea & Febiger, 1910.*)

This excellent manual has a well-deserved popularity. The fourth edition was favorably reviewed in this Journal (December, 1907) and the new edition is an improvement on the last. We again cordially recommend it to all who desire a small work on this subject.

The Essentials of Materia Medica and Therapeuties for Nurses. By JOHN FOOTE, M. D., Assistant Professor of Therapeutics and Materia Medica, Georgetown University School of Medicine. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

This volume of about 200 pages is designed, as its title indicates, to furnish a knowledge of the essentials of Materia Medica and Therapeutics. It is the view of the author that text-books on these subjects, written for the use of nurses, have often been too complicated and the task, on the part of the pupil nurse, of selecting the essential knowledge for the performance of the work, has been rendered unnecessarily difficult. The methods given for converting apothecaries' weights and measures into metrical weights and measures are clearly given and ought to relieve the minds of nurses of a serious burden. The descriptions of the actions of drugs and especially of the untoward effects of drugs are clear and terse. The book, as a whole, is a good one and will serve a useful purpose in the instruction of nurses.

Lippincott's New Medical Dictionary. A Vocabulary of the Terms Used in Medicine, and the Allied Sciences with their Pronunciation, Etymology and Signification. Including much Collateral Information of a Descriptive and Encyclopædic Character. By HENRY W. CATTELL, A. M. (Laf.), M. D. (U. of P.), etc. Freely illustrated with figures in text. Price $5. (*Philadelphia and London: J. B. Lippincott Company.*)

The character of modern dictionaries has very much changed from that of their early predecessors. To-day they are encyclopædic in character, and there is much more information to be found in them. This change, while valuable in many respects, has its dangers as well; the last edition of Webster's "New International Dictionary" is an example both of how a dictionary may be improved, and harmed by adding to it much information, which really belongs to an encyclopædia. This new medical dictionary shows the same advantages and disadvantages. Where the simple definition, derivation and use of words are not adhered to, there is no limit to what may be added or left out of a dictionary in the way of information; and so each will vary, depending on the editor. Lippincott's appears to be an excellent book, and if the user will first read the introduction (a task very few users of dictionaries will put themselves to) the use of the dictionary, and its values, will be much more readily comprehended.

Granting that the choice of his material and its use must be left to the editor, yet it may be permitted to make some reflections on certain points.

Why should French words, for instance, be found in an English dictionary? *e. g.—sonde*, its English equivalent, is just as good and there is no need to adopt this foreign word; *aï crépitant* is another example, and also *aboiement*.

It seems mere waste of space to name all the varieties of sutures, or to give all the names of different organisms to which syphilis has been attributed under the title Bacillus of Syphilis, since today we know that there is one and only one organism which causes this disease.

Under the headings "regio," "abscess," "hyper," and "malignant" we find all sorts of combinations which any school boy ought to understand without needing to look them up in a dictionary. To omit these would save much space.

Other compound terms like "pin-hole pupil," and "school-made chorea" might, it seems to us, be fitly omitted.

The gold-tail moth, with a reference to the Lancet, is unknown to us, while the brown-tail variety is now known to all the Eastern States and causes a dermatitis. To the latter variety there is no reference. As mere misprints we note under "sweat-fever" its definition anglicus sudor [sic]; under sweating-fever, Anglicus Sudor [sic], and on page 653, under the illustration of opisthotonos, occurs "Grande hysteria" which either should be grand hysteria or *grande hystérie*.

The illustrations are as a whole of almost no value, but otherwise the book, as a piece of book-making, is most satisfactory.

Practical Nursing. For Male Nurses in the R. A. M. C. and Other Forces. By MAJOR E. M. HASSARD, R. A. M. C., and A. R. HASSARD. Price $1.50. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

This book, with slight modifications, could be well used by any army medical corps, whether male or female nurses are employed. It has been carefully prepared and covers the ground satisfactorily. In a later edition, to make the work more generally serviceable, it would be well to omit such terms as "Higginson syringe' or "Neville cradle" as these names mean nothing to the

foreigner. It seems doubtful whether such large doses of brandy, as are mentioned on p. 228, for a child should ever be used, and the dose of diphtheria antitoxin for a child is usually less—not "the same" (p. 287) as for an adult. It is stated (p. 238) that the orderly in dressing a case of cancrum oris is allowed to smoke as the odor is nauseating. Female nurses do not smoke, and there is no good reason why male nurses should when so occupied. The directions for counting sponges (p. 200) before and after an operation are not the best control against leaving one in the abdominal cavity. "Practical Nursing" is none the less a thoroughly good and reliable guide.

A Text-Book of Pathology. By JOSEPH MCFARLAND, M. D., Professor of Bacteriology and Pathology in the Medico-Chirurgical College, Philadelphia, etc. Second Edition. (*Philadelphia: W. B. Saunders & Co., 1910.*)

The general arrangement of this book corresponds to that of the first edition. Aside from a differentiation into general and special pathology there seems to be very little selection in the grouping of subjects especially in the first half of the book. After discussing the pathology of nutrition and circulation in such detail as one could hardly expect to find in a book of this size, the author gives us a brief description of the cell and its life and follows this by three chapters on Regenerative, Retrogressive and Progressive tissue changes. In the first of these the healing of wounds is briefly considered, in the second aplasia and hypoplasia are separated by pages on infiltrations (fat, glycogen, serum, calcium, bone—under this, neoplasm—pigment) and degeneration, (fatty parenchymatous, etc.) from the paragraph on atrophy. This is followed by necrosis. In the third hypertrophy and tumor formation are discussed. Such an arrangement marks a radical departure from the customary arrangement and without any explanatory note seems to offer no advantages.

This is emphasized later. Inflammation and repair usually considered together are as we have seen separated. Repair is first considered under regenerative tissue changes and inflammation the natural precursor of repair only follows hundreds of pages later under the ambiguous heading of infection and infectious diseases. Even allowing this,. the chapters on inflammation leave one disappointed for the author devotes pages to the morphology and cultural characteristics of the organisms concerned in the process and relatively little to the parts of the subject usually liberally discussed. Throughout the book this portion of the subject is unsatisfactory and cannot compare with such presentations of the subject as Adami and others offer.

The second half of the book on Special Pathology is hardly more satisfactory. Let us analyze the chapter on Diseases of the Cardio-Vascular System. Without any preliminary embryological consideration the author plunges us into the malformations which are only comprehensible from a developmental aspect. Pericarditis follows and the presentation lacks unity and sequence to such an extent that the reader finds himself with a few isolated facts which should be related but are not, and so on through the myocardium. The fatty heart which on section allows oil droplets to escape and which imperils the life of the individual, the parenchymatous myocarditis which results in death from cardiac palsy and the myomalacia cordis which the author emphasizes are to say the least rare. The lack of histological description is most striking. In this chapter histological description of an antemortem clot and its mode of formation is not even hinted at (this is also very summarily discussed in the discussion of Thrombosis and Embolism in the General Pathology). This is in strong contrast to the pages devoted to pathological physiology of cardiac diseases with descriptions and tables of the murmurs.

The book is rather profusely illustrated. Many of these are borrowed, and these are the best. On page 117 there is a very good drawing by Chase of an hemorrhagic infarct. This same picture is later reproduced (p. 171) as an anæmic infarct. The object of this is obscure. The great dearth of histological illustrations, some 40 odd in the portion of the book devoted to Special Pathology, is striking and even these few do not compare with such illustrations as are found in Woodhead's Manual.

Briefly the arrangement of the book is original but unsatisfactory. The style is laborious and the excess of definitions in many places gives the book a dictionary-like aspect. In some instances the routine enumeration of causes, etc., may be of value. The attempt to cover the science of medicine in a text-book of Pathology has resulted in chapters on Parasitology, Clinical Microscopy, Bacteriology, Immunity and Clinical Diagnosis thus crowding the portions on pathological anatomy with the result that this portion of the book is inadequate. Important, even if unsettled, problems are not discussed, and the newer literature has been overlooked.

After a careful study of the work we feel that there are better pathologies for students, and that it needs careful revision to make it not only useful, but to correct its errors and bring it up to date.

A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease. By ARTHUR R. CUSHNY, M. A., M. D., F. R. S., etc. Fifth Edition. Thoroughly Revised. Illustrated. Price $3.75. (*Philadelphia and New York: Lea & Febiger, 1910.*)

The fourth edition of this work was reviewed in the May, 1906, number of this journal, and its admirable qualities were pointed out. This present edition is an improvement on the last for it is brought thoroughly up-to-date, and therefore it may be endorsed with all the warmth it received before, and recommended to students and practitioners as the best work in English on this subject.

The Diseases of Women. A Hand-Book for Students and Practitioners. By J. BLAND-SUTTON, F. R. C. S. Eng., etc., and ARTHUR E. GILES, M. D., F. R. C. S. Edin., etc. Sixth Edition. Illustrated. Price $3.25. (*New York: Rebman Company, 1910.*)

The success of this manual is deserved; it was warmly reviewed in this journal (April, 1907), and this edition is an improvement on the last, as new and important chapters have been added in "Injuries to the Uterus," "Fibrosis Uteri," "Adenomatous Disease of the Uterus," "Vermiform Appendix," and "Injuries to the Ureters." It is an art to write a good manual, of which the number is limited, and this is one of the best in any specialty.

Clinical Commentaries. Deduced from the Morphology of the Human Body. By PROFESSOR ACHILLE DE-GIOVANNI, Director of the General Medical Clinic, University of Padua. Translated from the Second Italian Edition by JOHN JOSEPH EYRE, M. R. C. P., etc. Part—General. Price $4.50. (*New York: Rebman Company, 1910.*)

That the morphology of the human body should be studied as a help both in physiology and pathology will be denied by no wise physician, but that these "Commentaries" can be correctly drawn from such a study is very doubtful. The chapter on the "Morphological Examination of the Heart" is very typical of the author's point of view, and so it is fair to make certain extracts to indicate his methods. On pages 221-224 is described how to mark out the cardiac triangle on the surface of the body—the description is vague, which is explained in the following statement (p. 224): "I have already said more than once that I have no faith in averages, and I have given my reasons. Hence I have considered it useless to give the figures which concern the length of the sides of the cardiac triangle." Morphology, if it is to be studied like other exact sciences, must deal with figures and averages. Some of the difficulty met with in understanding the

author may come from the very imperfect translation. On p. 225 occurs the following sentence: "The part which this contributes to forming the base and the apex naturally increases somewhat the proportion of the base and of the left ventricle; but at any rate in the maximal disproportion which refers to the right ventricle rests the criterion for concluding that the cause for the complexive enlargement of the heart is due both the right ventricle by reason of the entity of the disproportion of the side of the triangle which appertains to it." The author (p. 226), in italics, gives a method of measuring the fist and says if this is accurately taken "*one will have the measurement of the base of the heart.* This is a fact, not an opinion, ..." Throughout the work the author shows this unjustifiable (?) dogmatism. For instance, on page 96, we read "Following these conceptions, one comprehends that the external environment can modify the internal environment—that the diplococcus, for instance, of the saliva can become the penumococcus of pneumonia, and another the meningcoccus . . . ."

From the chapter on "*Fat and Panniculus Adiposus*" the following statements are taken: "and equally that the individuals in whom fat is produced beyond the ordinary amounts in some parts of their body demonstrate in these parts a morphological anomaly with a lymphatic character"; and further on "I have observed that in all ages the richness in fat coincides with a particular form of the body in which certain morphological relations that I shall indicate later on are always verified." One more quotation and we will close leaving it to those interested to decide as to whether the case is proven, as the author presents it, and whether so much can be deduced from morphology as he believes. "On the other hand, the growth of the trunk takes place less rapidly in the female sex than in the male, and this is in relationship with the great nervousness of females with scrofulous and rachitic constitutions. Without entering now into the discussion as to the importance of these ideas, it will be sufficient to state that we are dealing with the results of researches conducted without method [*sic*] with the sole object of finding averages [in which elsewhere the author has no faith], and not of forming series, according to the requirements of the morphological method, and that, notwithstanding this, from the results we see arise the importance which a new study of the vertebral column must have for recognizing the variations of its development in relationship with the whole of the body, including the medulla spinalis" (p. 157).

Vaccine Therapy—Its Theory and Practice. By R. W. Allen, M. D., B. S. (Lond.), etc. Third Edition. Price $2. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

The author states in his preface to this edition that "it has been completely rewritten and brought up to date." It has filled a want and been successful, and will doubtless continue to do so. We refer our readers to the very favorable notice of it which appeared in this Bulletin in March, 1909.

Practical Obstetrics. By E. Hastings Tweedy, P. R. C. P. I., and G. T. Wrench, M. D. Second Edition. Price $5.50. (*London. Henry Frowde and Hodder & Stoughton, 1910.*)

The first edition of this work appeared in 1908 under the title of "Rotunda Practical Midwifery" and was reviewed in this journal in December, 1909. What was said of it then applies today. It is a mistake to have changed the title. "The chapters on the toxæmia of pregnancy, uterine inertia, and contracted pelvis have been rewritten." Some other changes have been made in the book, and it is now a smaller volume, although the number of pages remains the same.

BOOKS RECEIVED.

Oxford Medical Publications. A System of Syphilis. In Six Volumes. Edited by D'Arcy Power, M. B. Oxon., F. R. C. S. and J. Keogh Murphy, M. C. Cantab., F. R. C. S. With an Introduction by Sir Jonathan Hutchinson, F. R. S. Vol. IV. Syphilis of the Nervous System. By F. W. Mott, M. D., F. R. S., F. R. C. P. 1910. 8vo. 502 pages. Henry Frowde, London; Hodder & Stoughton, London.

Diseases of the Colon and Their Surgical Treatment. (Founded on the Jacksonian Essay for 1909.) By P. Lockhart Mummery, F. R. C. S. Eng., B. A., M. B., B. C. Cantab. Illustrated by colored and other plates, and numerous figures in the text, many of which are reproduced from the author's sketches. 1910. 8vo. 322 pages. John Wright and Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent and Co., Ltd., London.

Light Therapeutics. A Practical Manual of Phototherapy for the Student and the Practitioner. With Special Reference to the Incandescent Electric-Light Bath. By J. H. Kellogg, M. D. 1910. 8vo. 217 pages. The Good Health Publishing Company, Battle Creek, Michigan.

Education in Sexual Physiology and Hygiene. A Physician's Message. By Philip Zenner. 1910. 16mo. 126 pages. The Robert Clarke Company, Cincinnati.

Treatises on Fistula in Ano, Hæmorrhoids and Clysters. By John Arderne, from an Early Fifteenth-Century Manuscript Translation. Edited, with introduction, notes, etc., by D'Arcy Power, F. R. C. S. Eng. 1910. 8vo. 156 pages. Published for the Early English Text Society, Kegan Paul, Trench Trübner & Co., Ltd., London; Henry Frowde, London and New York.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume II. June, 1910. 8vo. 363 pages. Lea & Febiger, Philadelphia and New York.

The Vegetable Proteins. By Thomas B. Osborne, Ph. D. 1909. 8vo. 125 pages. [Monographs on Biochemistry. Edited by R. H. Aders Plimmer, D. Sc., and F. G. Hopkins, M. A., M. B., D. Sc., F. R. S.] Longmans, Green and Co., London, New York, Bombay and Calcutta.

The Practice of Midwifery. Being the Seventh Edition of Dr. Galabin's Manual of Midwifery. Greatly Enlarged and Extended. By Alfred Lewis Galabin, M. A., M. D. Cantab.; F. R. C. P. Lond.; and George Blacker, M. D., B. S. Lond.; F. R. C. S. Eng.; F. R. C. P. Lond. Illustrated with 503 engravings. 1910. 8vo. 1123 pages. The Macmillan Company, New York.

Medical Education in the United States and Canada. A Report to the Carnegie Foundation for the Advancement of Teaching. By Abraham Flexner. With an Introduction by Henry S. Pritchett, President of the Foundation. Bulletin No. 4. 1910. 4to. 346 pages. D. B. Updick, The Merrymount Press, Boston.

American Practice of Surgery. A Complete System of the Science and Art of Surgery, by Representative Surgeons of the United States and Canada. Editors: Joseph D. Bryant, M. D., LL. D. Albert H. Buck, M. D. Complete in Eight Volumes. Profusely Illustrated. Volume Seven. 4to. 961 pages. William Wood and Company, New York.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Volume II. Twentieth Series. 1910. 8vo. 304 pages. J. B. Lippincott Company, Philadelphia.

Transactions of the Luzerne County Medical Society. For the Year ending Dec. 31, 1909. Volume XVII. 8vo. 228 pages. 1910. Wilkes-Barre, Pa.

Metropolitan Asylums Board. Annual Report for the Year 1909. (12th year of issue) 1910. 8vo. 271 pages. Chas. Straker & Sons, Limited, London.

Studies from the Rockefeller Institute for Medical Research. Reprints. Volume X. 1910. 8vo. 225 pages. New York.

Bulletin of the Warren Anatomical Museum. Harvard Medical School. No. 1. Pathological Anatomy. Bones. Joints. Synovial Membranes. Tendons. 1910. 67 pages. Boston, Mass.

What You Ought to Know About Your Baby. By Leonard Keene Hirshberg, B. A., M. D. A Text-Book for Mothers on the Care and Feeding of Babies, with Questions and Answers Especially Prepared by the Editor. 1910. 8vo. 97 pages. The Butterick Publishing Company, New York.

Refraction and Motility of the Eye. With Chapters on Color Blindness and the Field of Vision. By Ellice M. Alger, M. D. With one hundred and twenty-two illustrations. 1910. 12mo. 380 pages. F. A. Davis Company, Philadelphia.

Hand-Book of Electro-Therapeutics. By William James Dugan, M. D. With ninety-one illustrations. 1910. 8°. 242 pages. F. A. Davis Company, Philadelphia.

Essentials of Laboratory Diagnosis. By Francis Ashley Faught, M. D. Second revised edition. Containing an indican scale in colors, eight full-page plates and numerous engravings in the text. 1910. 8vo. 336 pages. F. A. Davis Company, Philadelphia.

A Manual of Physiology. With Practical Exercises. By G. N. Stewart, M. A., D. Sc., M. D. Edin., D. P. H. Camb. With colored plates and 450 other illustrations. Sixth edition. 1910. 8vo. 1064 pages. William Wood and Company, New York.

A Treatise on Orthopedic Surgery. By Royal Whitman, M. D. Fourth edition, revised and enlarged. Illustrated with six hundred and one engravings. 1910. 8vo. 908 pages. Lea & Febiger, Philadelphia and New York.

Gynécologie Opératoire. Par Henri Hartmann. Avec 422 figures dans le texte dont 80 en couleur. 1911. 4to. 498 pages. G. Steinheil, Paris.

Hernia. Its Cause and Treatment. By R. W. Murray, F. R. C. S. Second edition. With 62 illustrations. 1910. 8vo. 184 pages. J. & A. Churchill, London.

Osteology and Syndesmology. By Howard A. Sutton, A. B., M. D. and Cecil K. Drinker, B. S. 1910. 8vo. 225 pages. P. Blakiston's Son & Co., Philadelphia.

Report on the Measures Taken Against Malaria in the Lahore (Mian Mir) Cantonment. By the Hon'ble Mr. R. Nathan, C. I. E., I. C. S., Lieutenant-Colonel H. B. Thornhill, C. I. E., I. A., and Major L. Rogers, M. D., F. R. C. P., F. R. C. S., I. M. S. 1909. 8vo. Fol. 55 pages. 1910. Superintendent Government Printing, Calcutta, India.

Proceedings of the Sixteenth Annual Convention of the American Society of Superintendents of Training Schools for Nurses. Held at New York, May 16 and 17, 1910, and in conjunction with the Associated Nurses' Alumnæ of the United States, in the auditorium in the Horace Mann School, May 18, 1910. 8vo. 234 pages. J. H. Furst Company, Baltimore.

Diseases of the Stomach and Upper Alimentary Tract. By Anthony Bassler, M. D. Copiously illustrated with numerous half-tone and line text-engravings and 56 full-page half-tone plates (with nearly 100 figures) plain and in colors, from original photographs and drawings. 1910. 8vo. 836 pages. F. A. Davis Company, Philadelphia.

Oxford Medical Publications. Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following four volumes.

Fractures and Their Treatment. By J. Hogarth Pringle, M. B. (Ed.), F. R. C. S. (Eng.) Glasgow. 1910. 8vo. 384 pages.

A Handbook of the Surgery of Children. By E. Kirmisson. Translated by J. Keogh Murphy, M. C. (Cantab.), F. R. C. S. 1910. 8vo. 822 pages.

A System of Syphilis. In Six Volumes. Edited by D'Arcy Power, M. B. Oxon., F. R. C. S., and J. Keogh Murphy, M. C. Cantab., F. R. C. S. With an Introduction by Sir Jonathan Hutchinson, F. R. S. Vols. V and VI. 1910. 8vo.

Practical Physiological Chemistry. A Book Designed for Use in Courses in Practical Physiological Chemistry in Schools of Medicine and of Science. By Philip B. Hawk, M. S., Ph. D. Third edition, revised and enlarged. With two full-page plates of absorption spectra in colors, four additional full-page color plates and one hundred and twenty-seven figures of which twelve are in colors. 1910. 8vo. 440 pages. P. Blakiston's Son & Co., Philadelphia.

Rational Hydrotherapy. A Manual of the Physiological and Therapeutic Effects of Hydriatic Procedures, and the Technique of their Application in the Treatment of Disease. By J. H. Kellogg, M. D. With two hundred and ninety-three illustrations, nineteen in colors. Fourth revised edition. 1910. 8vo. 1247 pages. F. A. Davis Company, Philadelphia.

Die Faeces des Säuglings und des Kindes. Die Bedeutung und Technik ihrer Untersuchung. Von Dr. Adolf F. Hecht. Mit einen Vorwort von Hofrat Prof. Dr. Th. Escherich. 1910. 4to. 186 pages. Urban & Schwarzenberg, Berlin and Wien.

Andreas Vesalius, the Reformer of Anatomy. By James Moores Ball, M. D. 1910. Fol. XVII + 149 pages. Science Medical Press, Saint Louis.

Golden Rules of Refraction. By Ernest E. Maddox, M. D., F. R. C. S. Ed. "Golden Rules" Series. No. XII. Third edition, revised. 32mo. 96 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

Chronicles of Pharmacy. By A. C. Wootton. Two Volumes. 1910. 8vo. Macmillan and Company, Limited, London.

Applied Anatomy. The Construction of the Human Body Considered in Relation to its Functions, Diseases and Injuries. By Gwilym G. Davis. With six hundred and thirty illustrations, mostly from original dissections and many in color by Erwin F. Faber. [1910.] 4to. 630 pages. J. B. Lippincott Company, Philadelphia and London.

The Classification and Treatment of Diseases Commonly Known as Rheumatism. By Frank E. Peckham, M. D. Fiske Fund Prize Dissertation. No. LIII. 1910. 8vo. 76 pages. Snow & Farnham Company, Printers, Providence.

The Harvey Lectures. Delivered under the Auspices of The Harvey Society of New York, 1908-1909. By Prof. A. Calmette, Prof. W. G. MacCallum, Prof. Graham Lusk, Prof. W. Falta, Dr. John F. Anderson, Dr. M. J. Rosenau, Prof. A. B. Macallum, Prof. J. B. Leathes, Prof. Philip Hanson Hiss, Jr., Dr. C. B. Davenport. 1910. 8vo. 290 pages. J. B. Lippincott Company, Philadelphia and London.

Bier's Text-Book of Hyperæmia as Applied in Medicine and Surgery. By Professor Dr. August Bier. Only authorized translation from the sixth German revised edition by Dr. Gustavus M. Blech. With thirty-nine illustrations. [1909.] 8vo. 439 pages. Rebman Company, New York.

A Laboratory Text-Book of Embryology. By Charles Sedgwick Minot, LL. D. (Yale and Toronto), D. Sc. (Oxford). Second edition, revised with 262 illustrations, chiefly original. 1910. 4to. 402 pages. P. Blakiston's Son & Co., Philadelphia.

Vaccine Therapy. Its Theory and Practice. By R. W. Allen, M. D., B. S. (Lond.). Third edition. 1910. 8vo. 277 pages. P. Blakiston's Son & Co., Philadelphia.

The Diseases of Women. By J. Bland-Sutton, F. R. C. S. Eng., and Arthur E. Giles, M. D., B. Sc. Lond., F. R. C. S. Edin. Sixth edition, with 123 illustrations. [1909.] 12°. 554 pages. Rebman Company, New York.

Clinical Commentaries Deduced from the Morphology of the Human Body. By Professor Achille De-Giovanni. Translated from the second Italian edition by John Joseph Eyre, M. R. C. P., L. R. C. S. I., D. P. H. Cambridge. Part General. 8vo. 436 pages. Rebman Company, New York.

A Text-Book of Mental Diseases. By Eugenio Tanzi. Authorized translation from the Italian by W. Ford Robertson, M. D., C. M., and T. C. Mackenzie, M. D., F. R. C. P. Edin. [1909.] 8vo. 803 pages. Rebman Company, New York.

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The Lister Institute of Preventive Medicine. Collected Papers. No. 6. 1909-1910. 8vo. London.

Annual Report of the Sub-Department of Health Department of Public Safety. To the Mayor and City Council of Baltimore for the Fiscal Year ended December 31, 1909. 8vo. 243 pages. 1910. Meyer & Thalheimer, Baltimore.

A Manual of Human Embryology. Written by Charles R. Bardeen, Herbert M. Evans, Walter Felix [and others]. Edited by Franz Keibel and Franklin P. Mall. In Two Volumes. Volume I. With 423 illustrations. 1910. 4to. 548 pages. J. B. Lippincott Company, Philadelphia and London.

Normal Histology. With Special Reference to the Structure of the Human Body. By George A. Piersol, M. D., Sc. D. 438 illustrations, many of which are in colors. Eighth edition. (Re-written.) [1910.] 8vo. 418 pages. J. B. Lippincott Company, Philadelphia and London.

Lippincott's New Medical Dictionary. A Vocabulary of the Terms used in Medicine and the Allied Sciences, with their Pronunciation, Etymology and Signification. By Henry W. Cattell, A. M. (Laf.), M. D. (U. of P.) Freely illustrated with figures in the text. 1910. 8vo. 1108 pages. J. B. Lippincott Company, Philadelphia and London.

The Surgery of Childhood Including Orthopædic Surgery. By De Forest Willard, A. M., M. D. (Univ. of Pa.), Ph. D. With 712 illustrations, including 17 in colors. [1910.] 8vo. 800 pages. J. B. Lippincott Company, Philadelphia and London.

Scientific Memoirs. New Series, No. 37. By Officers of the Medical and Sanitary Departments of the Government of India. *Investigations on Bengal Jail Dietaries, with some Observations on the Influence of Dietary on the Physical Development and Well-being of the People of Bengal.* By Captain D. McCay, M. B., B. Ch., B. A. O., I. M. S. 1910. 4to. 226 pages. Superintendent Government Printing, Calcutta, India.

Cystoscopy as Adjuvant in Surgery. With an Atlas of Cystoscopic Views and Concomitant Text for Physicians and Students. By Staff-Surgeon Dr. O. Rumpel. Only authorized English translation by P. W. Shedd, M. D. With 85 illustrations in color on 36 plates and 22 texual figures. 1910. 4to. 131 pages. Rebman Company, New York.

The Priciples of Pathology. By J. George Adami, M. A., M. D., LL. D., F. R. S. Volume I. General Pathology. Second edition, revised and enlarged with 329 engravings and 18 plates. 1910. 8vo. 1027 pages. Lea & Febiger, Philadelphia and New York.

Symptomatic and Regional Therapeutics. By George Howard Hoxie, A. M., M. D. With fifty-eight illustrations in text. 1910. 8vo. 499 pages. D. Appleton and Company, New York and London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume III. September, 1910. 8vo. 338 pages. Lea & Febiger, Philadelphia and New York.

A Manual of Hygiene and Sanitation. By Seneca Egbert, A. M., M. D. Fifth edition, enlarged and thoroughly revised. Illustrated with 97 engravings. 1910. 12mo. 508 pages. Lea & Febiger, Philadelphia and New York.

A Treatise on Diseases of the Eye. By John Elmer Weeks, M. D. With 528 engravings and 25 full-page plates in colors. 1910. 8vo. 944 pages. Lea & Febiger, New York and Philadelphia.

The Practice of Medicine. A Guide to the Nature Discrimination and Management of Disease. By A. O. J. Kelly, A. M., M. D. Illustrated. 1910. 8vo. 945 pages. Lea & Febiger, Philadelphia and New York.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Volume III. Twentieth Series. 1910. 8vo. 311 pages. J. B. Lippincott Company, Philadelphia and London.

Claims Arising from Results of Personal Injuries. The Relation Injury Bears to Disease and Disease to Injury. By W. Edward Magruder, M. D. 1910. 12mo. 266 pages. The Spectator Company, New York.

Pathogenic Micro-Organisms Including Bacteria and Protozoa. By William Hallock Park, M. D., and Anna W. Williams, M. D. Fourth edition, enlarged and thoroughly revised. With 196 engravings and 8 full-pages plates. 1910. 8vo. 670 pages. Lea & Febiger, New York and Philadelphia.

The Essentials of Histology. Descriptive and Practical. By E. A. Schäfer, M. D., Sc. D., LL. D., F. R. S. Eighth edition. 1910. 8vo. 571 pages. Lea & Febiger, Philadelphia and New York.

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UNIVERSITY OF ILLINOIS

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OF

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LECTURES ON THE HERTER FOUNDATION.*

By Professor Hans Chiari, M. D.,

Professor of Pathological Anatomy, University of Strassburg, Germany.

I. The Relation of the Amnion to the Origin of Human Malformations.

If the pathologist would discuss the relation of the amnion to the origin of human malformations, he must base his views upon evidence gathered from pathological anatomy. He must study carefully the cases in point that he may recognize the variety of influences which the amnion can exert. He must seek industriously to ascertain causes for these pathological influences. Finally, from his own experience and that of others recorded in the literature, he must gain a correct view concerning the frequency of deformities which depend upon the amnion and must contrast them with deformities which arise in a different way.

Certainly, no one denies that human malformations may originate in other ways and quite independently of the amnion. Thus, we know a child may inherit a deformity from either its paternal or its maternal ancestors: polydactylism illustrates that fact. The cause for such malformations exists in the germ cells—either ovum or spermatozoon. Again, some disease of the embryo may occasion malformation which is exemplified by pathological collections of fluid within the body cavities (Höhlenhydrops). Occasionally, the umbilical cord or the second ovum where there is a double pregnancy, will exert a teratological influence. We also know that an injury directed against the abdomen of a pregnant woman may bring about fœtal malformation. To demonstrate the efficiency of this last influence I will relate the history of a case which I saw in the year 1881, while in Vienna, and which was published by Anton. The infant was a boy who died when fourteen days old. The autopsy revealed an imperfect corpus callosum; persistence of the embryonic median furrows of the cerebrum with microgyria; hair lip and cleft palate; and a fracture of the right femur which had healed in utero. The period at which the defect in the corpus callosum must have originated was the beginning of the fourth month of pregnancy. At this time, moreover, according to the mother's history, she had sustained an injury, falling on the ice in such a way as to receive the brunt of the blow upon her abdomen. This had caused the fracture of the femur, and favors Anton's view, that the same injury caused not only breaking of the bone, but also malformation of the brain. The pathologist who studies human malformations of amniotic origin, must do so in the light of both comparative pathology and experimental teratology. But he will be very careful in adopting their teaching, since the origin and significance of the amnion are not the same in man and in the lower animals.

* Delivered in the Medical Department of the Johns Hopkins University, October 5, 6, 7, 1910.

I have had opportunity to study an unusually large number of human malformations. The cases, I shall bring to your attention are selected from this material, which was secured at the Universities of Prague and Strassburg.

By far the most common human deformities of amniotic origin are those caused by "Simonart's bands." These string-like portions of amnion usually pass from that membrane to the embryo. A great deal has been written about the malformations they cause. Such deformities represent widely different types, including hair lip, cleft palate, micrognathia; fissure of the face, of the brain, of the spinal cord; fissure of the thorax and of the abdomen; constriction of the penis, and malformation of the extremities.* These bands run not only from the amnion to the fœtus, but may pass from one part of the surface of the fœtus to another. It has been satisfactorily demonstrated that subsequent development of the embryo or fœtus may cause the amniotic bands to disappear after they have produced deformity; hence their previous existence may be attested at the time of birth only by the damage they have worked.

I am indebted to Professor Kretz for permission to use the following cases from the Pathological Museum at Prague:

Fig. 1 shows both hands of a nine-month fœtus with perodactylia caused by Simonart's bands; in other respects it was normal. On the left hand the fourth and fifth fingers, on the right hand the third, fourth and fifth fingers are imperfectly formed; the fingers mentioned on the right hand are not separated from one another. Remains of amniotic threads are seen on both hands, adherent to the affected fingers. We were unable to examine the placenta.

I have found the same kind of deformity in a woman seventy years old, and in her case the deformity was certainly caused by amniotic threads (Fig. 2). The right hand presents atrophy of the fourth and fifth fingers; the left hand, atrophy of the fourth and fifth fingers, together with a defective nail on the fifth finger, a deep dorsal furrow on the fourth finger, a rather deep furrow on the back of the first phalanx of the third finger, and a furrow on the back of the second phalanx of the index finger. These deformities were all present at birth.

In proof of the fact that amniotic bands may cause constriction about more proximal parts of the extremity, I offer, as an example, the case pictured in Fig. 3, which is that of an infant who died when three hours old. It presented fissures of the brain and of the face. The left hand showed indentations upon the third, fourth and fifth fingers; absence of the nail phalanx of the fifth finger, at the ulnar edge of which there still hung a remnant of an amniotic thread. On the right side, and about 1 cm. below the elbow, a deep circular fissure was found; the constriction reached the neighborhood of the bones of the forearm. At this point the skin was rent and the bones were broken as the result of injury at the time of birth. Distalwards from this circular fissure were found the remains of an extremity. It measured 5 by 3½ cm., had an oval shape, and was covered with skin. This structure corresponded to the upper arm and the hand. It was markedly œdematous, and at its peripheral end bore four digits; three of them, namely, the fourth and fifth fingers and the thumb, were well formed, except that the nail on the last was lacking. All were of normal size. The second finger was represented by a short, pyramidal projection of skin without any nail, and had been drawn upwards and outwards to the side of the thumb. Amniotic threads joined the above mentioned constriction in the forearm to the rudimentary finger, and held the latter as would a sling. The third finger was entirely lacking.

It would have been only a step from this deep circular fissure formation to complete intrauterine amputation of the right forearm. In this instance also, we had no opportunity to examine the placenta.

Much less frequently, amniotic bands are found attached to other parts of the body. Fig. 4 shows a shrivelled, sixth-month fœtus papyraceous, which had died sometime before birth. Amniotic adhesions appear on the head. A band 4 cm. long and 2 mm. thick extended from the skull of the fœtus to a point on the placenta near the insertion of the umbilical cord, and was twisted in a spiral about the latter structure. A club-shaped appendage was found in the region of the large fontanelle, immediately in front of the amniotic band with which it was connected. The appendage was 1 cm. long, and 5 mm. thick at its free end. It was covered with skin, contained a cavity which could be traced through its pedicle into the cavum cerebri, and clearly represented an encephalocele. The periphery of the placenta had involuted and completely atrophied; but for that, the amnion presented its normal characteristics.

In this case, then, we have seen an amniotic band attached to the head of an embryo and an encephalocele produced through the traction thus occasioned. Moreover, fœtal death was very likely the result of its action, since constriction of the umbilical cord by the band would seem to account for that event.

Figure 5 represents a case of schizosoma caused by amniotic bands. The fœtus was about 38 cm. long. A short, ribbon-like band of amnion passed from the region of the navel to the back of the fœtus and had drawn along a tongue-shaped projection of skin with a small, round cutaneous appendage upon it. In consequence of this band, several deformities had arisen, namely, a deep transverse furrow across the back; imperfect closure of the pleuro-peritoneal cavity on the right side; protrusion of the viscera; and defective formation of the right upper extremity. There was no umbilical cord. The umbilical arteries and the umbilical vein issued from the lower edge of the abdominal fissure. These vessels were closely approximated, and ran to the placenta surrounded by a very small quantity of Whartonian jelly, which in turn was encased in amnion. The other malformations noted in this specimen were a median fissure of the thumb; talipes varus with heptadactylia on the left side and talipes valgus with hexadactylia on the right. A few amniotic threads hung upon the right

* See Von Winckel.

foot. The amnion which covered the placenta exhibited a few similar threads, scattered here and there over its inner surface.

Figure 6 illustrates the group of cases in which amniotic bands pass from one part of the fœtal body to another. This fœtus was 40 cm. long and of the male sex. An encephaloeelc, with a horizontal circumference of 22 cm. appeared upon the skull. The skin covering it was very thin; the hernial opening was 2.5 cm. wide; the cavity within the skull was quite small. A chilo-gnatho-palatoschisis appeared upon the right side of the face. From the chiloschisis a fissure ran upwards through the right half of the nose to the anterior edge of the hernial opening. A thread-like cord 10 cm. in length was attached at the latter point, and ran toward the right axilla, where it divided into three parts, one of which was attached to the anterior, and one to the posterior axillary fold; the third was attached to the baek near the lowcr angle of the right scapula. Furthermore, the right hand was deformed; the fingers from the second to the fifth were small, malformed, without nails and constricted by manifold, delicate amniotic threads. The last joint of the fourth finger on this hand had turned black. The right foot showed a valgus, and the left a varus position. The plaeenta was not obtained.

Pathological anatomy also teaches that the mediation of Simonart's bands is not the only way in which the amnion may be causally related to fœtal malformations; abnormality in the size of the amniotic cavity, and particularly a diminution thereof reacts harmfully upon the development of the embryo. Cases of this sort have been recorded by Marchand and by Schwalbe. In the case reported by Marehand, the embryo had attained six to seven weeks' development. Adhesions were present, but there was also a particularly defective amnion. It was through the latter anomaly that the embryo had suffered extensive deformation. A continuous layer of amniotic epithelium was seen upon the inner surface of the chorion. Marchand attributed this either to a late proliferation of the epithelium from the point where the amnion had ruptured, or to cleavage between the amnion and the chorion. Schwalbe's case pertained to a seven-month fœtus, in which abnormal contracture of the amnion had caused unusual bending of the body, extensive adhesions of different parts of the body, and a series of malformations.

In this connection, I am able to add another case, illustrated in Figs. 7a and 7b. This specimen consisted of a 34 cm. long, female fœtus, which presented fissure of the face, a scar together with two cylindrical eutaneous appendages upon the hydrocephalic skull and perodactylia of both hands as well as of the right foot; from the digits of the last remains of amniotic adhesions hung. Moreover, in this specimen we found a fissure involving the abdomcn and the lower part of the thorax. Most of the abdominal organs and the left lung projected through the opening. The trunk of the fœtus was conspicuously narrow, and gave the impression of having been squeezed in a corset. A thick, net-like covering of amnion, presenting many apertures, was fitted closely about the body, yet was not adherent save at the edges of the fissure. The umbilical cord entered at the right edge of the abdominal fissure. This structure was 13 cm. long, and was inserted upon the margin of the placenta, which had a diameter of 17 cm. The amniotic covering of the placenta, and indeed of the entire inner surface of the chorion was lacking. Microscopical study verified that faet, showing only a few delicate thread-like remnants of the membrane. The short umbilical cord was entirely covered by amnion.

From the findings in this specimen, the conclusion is unavoidable that the schizosoma had been produced by diminution in the size of the amnion. The body of the embryo had been surrounded by a closely applied corset which interfered with the closure of the pleuro-peritoneal cavity. The membrane had become detached in the neighborhood of the head and the extremities; these regions were separated from the rest of the amnion. Malformation of the head and extremities had been caused by Simonart's bands, remnants of which were attached to the inner surface of the chorion.

I found a specimen in the Prague Museum which probably belongs to this group of cases. The fœtus was a male, and had reached the fourth month of development. One could not actually demonstrate that the amniotic eavity had been contracted, but could prove that the cause of the deformity was abnormal pressure against the amnion in the locality of the affected parts (Fig. 8). The left upper extremity of the fœtus was rudimentarily developed, and supplied with only one digit. The limb was attached in a deep fossa upon the left wall of the thorax where the cartilages of the third, fourth and fifth ribs were absent, and the pectoralis major muscle, as well as the neighboring intercostal muscles, were very thin. In this instance, it seems fair to suppose that the amnion whieh enclosed the left upper extremity had been too small, and that perobrachia was produced in that way. Ritter, Ganghofner and Eppinger have described cases of the same character.

Viewed from the standpoint of pathological anatomy, it is not impossible that malformations and even death of the embryo may result from an abnormally spacious amnion, or to a premature collection of amniotic fluid. Yet, actual observations, so far as I know, have not been made to substantiate this opinion; nor have I observed cases which would seem to belong in that category.

What do we know concerning the cause and mode of formation of either Simonart's bands or of an abnormally small amniotic cavity?

Originally, Simonart's bands were thought due to an organization of lymph (Moutgomery), which was referred to some inflammatory process (Simpson, Gratzer, Simonart). Many authors, including Virchow, aeeepted the inflammatory hypothesis. In 1854, G. Braun expressed the view for the first time that Simonart's bands were in reality abnormally disposed portions of the amnion itself. He inferred that they originated in consequence of pathological folding of the amnion, and that this phenomenon, in turn, depended upon a seant quantity of amniotic fluid.

C. Braun explained the presence of these bands through the formation of plastic adhesions. Kustner elaborated the theory,

and suggested that intimate contact was established between the amnion and the embryo during the early days of development. He considered that narrowing of the amnion, a deficiency of amniotic fluid and the formation of folds in the membrane might bring about adhesions between it and the young embryo. These adhesions gradually became firmer and occasioned the malformation. Possibly, other outgrowths might later develop from the amnion, but in that event the epithelium covering the surface of the fœtus would have to die before adhesions could occur. Finally, Kustner believed that a deficiency of amniotic fluid made it possible to have secondary adhesions arise in connection with fissure formation when the epithelium of the medullary folds or of the intestinal wall was elevated. Later Kustner described a case of congenital amputation of hands and feet by amniotic threads, which resulted from a rent in the amnion due to the mother lifting a heavy load during the second month of pregnancy. The amnion had entwined itself about the umbilical cord, and entangled the extremities of the embryo, thereby affecting their amputation. Olshausen discussed tearing of the amnion as a source of amniotic threads, and concluded that the amnion may rupture spontaneously if its cavity be too small. Stoeckel has quite recently collected a series of these cases in which extra-amniotic pregnancy was associated with amniotic bands.

My own view is that adhesions between the epithelium of the amnion and the ectoderm of the fœtus are of primary importance in the formation of Simonart's bands. Although we are not as yet sufficiently familiar with the development of the amnion (Graf v. Spee holds the interesting view that the amniotic cavity in the human arises as a closed cavity within the blastodermic vesicle and develops from the ectoblast) still we know that it is formed very rapidly, since the youngest human ova which have been described already possess a closed amnion. Embryos of 10 mm. are closely surrounded by amnion. Embryos of 11-15 mm. are separated from the amnion by a distance of only 1-3 mm., and it is only when a length of more than 20 mm. has been attained that the quantity of amniotic fluid becomes commensurate with the size of the embryo, thus insuring an appropriate separation between it and the amnion (Marchand, Kollman).

With these facts in mind, it is not difficult to understand how the human embryo may become adherent to the amnion during the early weeks of pregnancy. The ectodermal cells on the inner surface of the amnion, as well as those covering the surface of the embryo, are young and active, and can fuse together easily if they are not sufficiently separated from one another. The union will gradually grow firmer. Later, when the amniotic fluid begins to develop, the adhesions are drawn out and become Simonart's bands, stretching from amnion to fœtus, or from one part of the fœtus to another. Inasmuch as these adhesions occur during the earliest stages of development they cause the most extreme types of deformity, one can imagine. This conception, which includes a primary adhesion and a later fusion of the two epithelial surfaces belonging respectively to the amnion and to the embryo, agrees perfectly with the histological findings in Simonart's bands. Microscopically, these bands consist of a wavy mass of amniotic connective tissue, exhibiting very few nuclei and no blood vessels. They are covered by amniotic epithelium which shades into the fœtal epidermis. As they approach the embryo, the covering of these bands often presents the typical structure of skin, from which we may infer that they ultimately draw out the skin, making it a part of the band.

In addition to the mode of formation just described, others occur, though much less frequently: thus, Simonart's bands may arise in consequence of rents in the amnion. This appears to me to support the interpretation of the previously mentioned case with corset-formation, which was attributed to contracture of the amnion combined with laceration of the membrane and the production of Simonart's bands.

Valuable contributions from the field of experimental teratology shed light upon the causation of narrowing of the amnion, and the mechanism by which it is produced. In this connection, reference should be made to the unusually interesting experiments of Dareste. By raising and lowering the temperature of an incubator, and by warming different parts of a hen's egg unequally, this investigator frequently succeeded in producing disturbances in the development of the amnion. Moreover, embryonic malformations, apparently of amniotic origin, were noted: cyclopia was occasioned by narrowing of the head-fold, and symelia by narrowing of the tail-fold. These experimental observations support the conception that narrowing of the amnion has a very direct bearing upon the origin of certain human malformations. To be sure, these results are not strictly analogous with similar human deformities, since the formation of the amnion in the chick and in man are essentially different. In the former, the amnion is formed by the union of the folds which arise at the anterior and posterior ends of the body as well as at either side. These folds meet and fuse over the back of the embryo. With this mechanism, it becomes very easy to have serious interference with development of the embryo, since either the head, the tail, or one of the side folds may not rise sufficiently, and thus fail to reach its proper destination. As a result of such aminotic defects, malformation of the embryo occurs.

In the development of the human ovum, according to His, the amnion is formed exclusively by the head-fold; this extends over the embryo toward the tail, and ultimately shuts in the amniotic cavity. None the less, here again it becomes entirely possible for the amnion to attain incomplete development through one harmful influence or another, and a pathological narrowing of the cavity may result. We can also imagine the amnion becoming abnormally firm and rigid in consequence of some disease; so that it is incapable of the distension requisite for the subsequent growth of the embryo. Of course that is only an hypothesis at present. We meet occasionally with cases which demonstrate that the amnion may undergo pathological thickening, and attribute it to an inflammatory change. In this connection, the interesting case of v. Franqué should be cited. There a number of wart-like nodules were noted on the fœtal side of the amnion, and near them superficial plaques were found. These had arisen through the proliferation of amniotic stroma about certain

products of the fœtal skin (vernix caseosa, desquamated epidermis, small clumps of lanugo hair), which had been deposited upon the amnion. Further, the fact should be mentioned that so-called "wind eggs"—a name given cases in which the embryo has perished—often present circumscribed or diffuse thickening of the amnion. Microscopically, the condition proves to be a proliferation of amniotic stroma and epithelium.

What proportion of human malformations can be fairly ascribed to an amniotic origin may be difficult to decide, but no doubt can exist that the number is large. Among 178 cases of malformation studied by v. Winckel, 29 cases (16.3 per cent) were referable to Simonart's bands. My own experience leads me to a similar conclusion. Beside this group, we have the other in which deformity is due to narrowing of the amniotic cavity; and the latter, according to my view, is at least as large as the former. Combining the two, I would attribute one-third of all human malformations to some influence exerted by the amnion. Such an estimate, moreover, does not take into account the deformities met with in cases of hydramnios.

Oftentimes, it becomes impossible to demonstrate the amniotic origin of malformations. On the one hand, it frequently happens that the membranes are studied too superficially, and on the other, Simonart's bands, as well as evidence of the narrowing of the amniotic cavity, may disappear in the latter months of pregnancy. For these reasons, it is desirable to collect a larger amount of material and study it more thoroughly than has been done.

In conclusion, I should like to speak of congenital defects, which occur in the skin, especially about the head, and have been referred to the traction of amniotic bands. Keller has recently reviewed cases of this sort and included a new example, which was observed in the Pathological Institute at Strassburg. The defect was located upon the skull, and differed, in one respect, from similar cases thus far reported. Microscopical examination in this instance showed that hair follicles were present at the site of the defect. That finding does not agree with the hypothesis that very early amniotic adhesions existed. Therefore, Keller, concluded, if the tearing loose of amniotic adhesions was to account for the deformity in his case, the adhesions must have developed after the fourth month and not during the early days of embryonic development. Moreover, he held that some inflammatory process was fundamentally responsible and his opinion had support in that the mother had suffered from endometritis. The placenta was firmly attached to the uterus and its separation was accomplished with difficulty. Such a case certainly suggests that inflammatory changes in the amnion be given careful consideration in future study of the development of the ovum.

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II. NECROSIS OF THE PANCREAS.

Necrosis of the pancreas may arise from many different causes. It may be due to a severe trauma, directly affecting the organ, as for example in gunshot wounds; or it may be caused by corrosive poisons, such as sulphuric acid, acting through the stomach wall. Again it may develop from the perforation of a petic ulcer of the stomach, or result from an inflammation of the pancreas, in so far as extensive necrosis and putrefaction may follow suppuration of the organ. It is my belief, however, that much the most common cause of necrosis of the pancreas is autodigestion due to the tryptic ferment of the pancreas.

The corrosive action of the pancreatic secretion has been known for a long time, and the tryptic autodigestion of the pancreas has been pointed out likewise. In 1879, Klebs attributed pancreatic hemorrhages to the corrosive action of pancreatic juice. Gussenbauer in 1883 described a cyst of the pancreas which had been formed by the destruction of a melanosarcoma by the pancreatic secretion. Arnozan and Vaillard referred in 1884 to the post mortem autodigestion of the pancreas in animals. Selzer (1886) and Wölfler (1888) thought that the erosion of the walls of pancreatic cysts by the pancreatic secretion might lead to hemorrhages. Pelliet (1889) and von Hansemann (1894) noted the frequency of post mortem autodigestion of the pancreas. Tilger (1894) attributed the origin of pancreatic cysts to autodigestion in pancreatitis. Nimier (1894) emphasized the importance of the pancreatic secretion as a source of pancreatic cysts, following injury to the duct of Wirsung. In 1895 I described the occurrence of intra-vitam, intra-agonal and post mortem auto-

digestion of the pancreas, and drew a comparison between this and peptic autodigestion of the stomach wall. Blume (1897) and Pförringer (1899) supported my views, and Blume, as well as Beneke, sought the cause for intra-vitam autodigestion in temporary ischæmia, and Pförringer in fat necrosis. I described in 1900 a case of focal intra-vitam autodigestion in all probability caused by arteritis obliterans. Gaylord (1901) reported autodigestion of the pancreas following gunshot wounds. In 1901 and 1902 Lazarus attributed anew the origin of pancreas cysts to autodigestion.

Numerous cases of intra-vitam tryptic autodigestion of the pancreas were, in my opinion, incorrectly interpreted, being described as hemorrhage of the pancreas, as pancreatitis hemorrhagica and gangrenosa (Fitz) and as necrosis of the pancreas from other causes. Here are to be found many pertinent observations, which resulted from investigation of cases of fat tissue necrosis by Balser (1882) which have since been proved to be due to a lipolytic ferment of the pancreas. The necrosis of the pancreatic tissue so frequently found has been considered, by most of the writers, as secondary in relation to the necrosis of the fat tissue, and even those authors who regarded the pancreas necrosis as primary, and the fat tissue necrosis as secondary, did not ordinarily think of a tryptic autodigestion as the cause of the pancreas necrosis, but rather assumed a primary pancreatitis. Only a few writers (Dettner, 1895; Hildebrand, 1898; Konheimer, 1898; Kaufmann, 1891) took the position that the spontaneous fat tissue necrosis was due to an intravital tryptic autodigestion, rather than to a traumatic rupture of the ducts of the pancreas. In 1902, I expressed myself firmly of the belief that both these conditions regularly belonged together, in the sense that the primary factor was the tryptic autodigestion of the pancreatic tissue, which was followed by the necrosis of the fat tissue, due to a pouring out of the fat ferment and its diffusion. I was also able to show that in post mortem and especially in intra-agonal autodigestion of the pancreas, it was not seldom the case that the fat tissue in the pancreas showed the beginning of the changes as they occur in necrosis of the fat tissue, and I explained further that the pancreas hemorrhages and pancreatitis acuta hemorrhagica and gangrenosa were nothing more than changes in the pancreas due to autodigestion. Necrosis is primary and possible inflammation is secondary. Then Weil (1904), Reitter (1905) and Truhart (1906) expressed similar opinions. In 1906 I maintained the view that the intra-vitam tryptic autodigestion of the pancreas might, *on the one hand,* be a most important process, leading to extensive hemorrhages in the pancreas and its neighborhood, to hemorrhagic cyst formation of the pancreas, to focal or diffuse necrosis of the pancreas and to suppurative pancreatitis and sequestration of the pancreas if pathogenic bacteria invaded it; but that *on the other hand* from circumscribed slight tryptic autodigestion of the pancreatic tissue, harmless, small areas of pancreas necrosis and fat tissue necrosis (secondary autopsy findings) might develop, which areas of pancreas necrosis might disappear entirely by absorption. But in view of this, tryptic autodigestion of the pancreas deserved the title of a *morbus sui generis.* Williams and Busch (1907), Truhart (1908) and most recently, Opic and Meakins (1910), have expressed similar views, so that the doctrine of the tryptic autodigestion necrosis of the pancreas seems to be well founded.

There is not the least doubt that the *causes for the occurrence of a "spontaneous" intra-vitam tryptic autodigestion* of the pancreas may be manifold. Anything which may lead to injury of the tissues of the pancreas or to activation of the tryptic zymogen, may induce tryptic autodigestion of the pancreas. I would call especial attention to the following important etiological factors: slight trauma of the pancreas, not causing rupture of a duct; disturbances of the pancreatic circulation, which may be looked upon (Benecke and Blume) as spastic anæmias, which may be caused by the frequently noted arteritis obliterans; stagnation of the pancreatic secretion; entrance of bile into the duct of Wirsung in cases of cholelithiasis, as was first shown by Halsted and Opic in 1901; and finally entrance of the secretions of the stomach, or the contents of the duodenum into the duct of Wirsung (Hess, 1903 and 1905; Beitzke, 1905). In individual cases one must always recall, and consider, as Eppinger showed in 1905, that the kinases which are able to activate the pancreatic secretion, may be of many different kinds. I will not deny that tryptic autodigestion of the pancreas may arise from a primary inflammation of the organ, but I think it happens rarely.

The consequences of tryptic autodigestion of the pancreas may vary widely. As I have mentioned, a grave disease may result. Death may result from severe hemorrhage—the so-called apoplexy of the pancreas. Within a few days death may follow after symptoms of ileus and peritonitis, when one usually finds extensive necrosis of the fat tissue in association with the reactive inflammatory necrosis of the pancreas. The cause of death in such cases is to be attributed either to a resorption of a pancreas toxin (Dobenauer, 1906) a product of necrosis, or to poisoning by trypsin (Guleke, 1906). Starting from the pancreas a diffuse abdominal tryptic destruction of the cellular tissue may arise, as I, myself, had opportunity to report in a case (1909). Suppuration and gangrene of the pancreas, with eventual sequestration of the organ, may develop. Cysts of the pancreas may form in consequence of the tryptic autodigestion. On the other hand, however, the tryptic autodigestion of the pancreas may be an insignificant process, which induces small circumscribed necrosis of the tissue of the pancreas, and small circumscribed areas of fat tissue necrosis. In the course of time all these foci may disappear, through absorption of the necrotic tissue, or at least of the foci of (necrotic) pancreatic tissue in which case we may conclude from the presence of old fat necrosis in the pancreas and its neighborhood that there has been an earlier autodigestion of the gland.

From all this it is easily seen what an important rôle the tryptic autodigestion of the pancreas plays. It is surely one of the most important factors in the pathology of this organ. The practicing physician must be cognizant of this autodigestion, since experience has shown that in the severe cases life oftentimes may be saved by surgical measures.

III. SPONDYLOLISTHESIS.

Following the enunciation by Kilian in 1853 that spondylolisthesis is a pelvic deformity resulting from a gradual gliding forward, or an olisthesis, of the inferior surface of the last lumbar vertebra over the anterior border of the first sacral vertebra, a large special literature has developed upon the subject.

The spondylolisthetic pelvis is of the greatest practical interest to the obstetrician on account of the part which it may play in the production of dystocia. On the other hand, the olisthesis demands attention from the pathological anatomist as an example of a peculiar acquired displacement of the vertebræ, whose mode of origin is not easy to understand.

Practically every case coming within this category has been described and published, so that Neugebauer, who devoted particular attention to its study was able to collect

11	clinical	and	12	anatomical	cases	in	1882
37	"	"	24	"	"	"	1885
47	"	"	53	"	"	"	1892
and 55	"	"	60	"	"	"	1893,

making a total of 115 cases. This, however, included 10 cases of olisthesis of the fourth lumbar vertebra, and one instance involving the first sacral vertebra. Furthermore, in 1899, Williams described a new specimen, and collected 123 cases from the literature, 62 of which were clinical and 61 anatomical. He also stated that Dr. Authur Dean Bevan had informed him that he had observed several cases in the dissecting room in Chicago.

According to Olshausen and Veit about 130 cases had been reported up to 1902, 70 of which were described anatomically and the remainder reported clinically.

Following the publication of Williams, and including his specimen, I have been able to collect 10 clinical and 7 anatomical cases, so that the entire number thus far recorded amounts to 146. At the same time, it must be admitted, particularly among the cases which were described clinically, that in not a few the diagnosis was at least doubtful. Moreover, in several specimens, which were described anatomically, only the pelvic portion of the vertebral column or even isolated vertebræ were available for study, so that Breus and Kolisko in 1900, in their monumental work on Pathological Forms of the Pelvis, after excluding the imperfect preparations, as well as those in which the olisthesis was only beginning, stated that only 18 examples of well-developed spondylolisthesis were on record, accompanied by a satisfactory anatomical description of the pelvis, and to these they added two additional specimens which they had discovered in Vienna.

Especially from a clinical point of view, the means of diagnosticating spondylolisthesis have been fully developed; and a series of characteristic symptoms described, such as the transverse furrow in the back above the lumbo-sacral juncture, the lumbar lordosis, the diminished pelvic inclination, and the peculiar "rope dancer gait" of the individuals affected by it. At the same time, the importance of lumbo-sacral spondylolisthesis has been accentuated on account of the important part it may play in reducing the size of the pelvis and thus interferring with the act of labor.

Anatomically the various changes in the shape of the bones and ligamentous structures have been described, and the effect of the olisthesis upon the form of the pelvis has been studied, more particularly by Breus and Kolisko. According to these authors, a fully developed spondylolisthetic pelvis is a "pelvis obtecta," which is composed of plump, massive bones. With the exception of the conjugata vera, the pelvic measurements are usually large. The former, however, as a result of the olisthesis, is markedly shortened, in that the antero-posterior diameter of the pelvic inlet, which takes the place of the vera, will impinge posteriorly upon the ventral surface of one of the prolapsed lumbar vertebræ, instead of upon the promontory of the sacrum. The pelvic inclination is also diminished, the upper end of the sacrum appears to be inclined posteriorly, and the region of the symphysis pubis elevated. Frequently, the vertical concavity of the sacrum is markedly increased and the entire bone is retroposed, and the articulation between the first and second sacral vertebræ gapes toward the sacral canal. The ilio-sacral joints are markedly developed, their ligaments strong and the acetabula deep. All of these changes are to be attributed to the forward displacement of the center of gravity of the body, and to the change in the manner in which the body weight is transmitted to the sacrum, and tend to become more and more pronounced until the olisthesis is checked by synostotic processes.

The most interesting question in connection with this subject is the mode of production of the olisthesis, and numerous theories have been advanced in the attempt to solve it. Kilian in his original communication considered that the most important etiological factor consisted in an inflammatory softening of the last intervertebral cartilage, as well as of the neighboring ligaments and vertebræ. At the same time, he admitted the possibility of spondylolisthesis developing as a result of retrogressive changes in the first sacral vertebra. Ritgen in 1854 expressed the belief that the anomaly might result from an œdematous condition of the spinal membranes, which had not led to the production of spina bifida (hydrorrhachis incolumnis).

Robert in 1855 was the first to resort to experiment in the hope of elucidating the etiology of lumbo-sacral spondylolisthesis, and showed that it never followed mere section of all the ligamentous structures about the lumbo-sacral juncture, but readily occurred after the interarticular portions of the arch of the last lumbar vertebra had been sawed through, and the last intervertebral cartilage severed. From these observations, he concluded that the development of lumbo-sacral spondylolisthesis is usually prevented by the articular processes, and can only occur after their destruction. Or, it might follow luxation of the inferior articular processes of the last lumbar vertebra, or finally be due to a general softening of the ring of the last lumbar vertebra which permitted its articular processes to become so far removed from its body that the latter could glide forward and downward, while its inferior

articular processes still remained in contact with the superior articular processes of the first sacral vertebra.

The hydrorrhachis theory was generalized by Lambl in 1856 and in 1858. He held that such a condition could give rise to a pseudoarthrosis of the interarticular portion of the last lumbar vertebra, which would lead to the formation of a spondylolysis interarticularis. At the same time, he admitted the possibility of spondylolisthesis lumbo-sacralis developing as the result of luxation of the lumbo-sacral articular processes, or from a fracture of the arch of the last lumbar vertebra, as well as from the presence of a rudimentary accessory vertebra (Schaltwirbel).

Breslau, in 1861, in describing a new case, designated as caries sicca an inflammatory softening of the bony tissue of the last lumbar and first sacral vertebræ, as well as of the last intervertebral cartilage; and stated that the lengthening of the vertebral arch in spondylolisthetic processes could therefore be secondary in nature. In 1863 Hugenberger attributed a case of traumatic lumbo-sacral spondylolisthesis to forcible luxation or fracture of the articular processes; while Blake in 1867 considered that the development of the olisthesis might be due to excessive stretching of the ligaments at the lumbo-sacral juncture resulting from lipomatosis universalis. Blasius and Ender in 1868 and 1869, respectively, contended that their cases should be attributed to lumbar caries.

The idea that spondylolisthesis lumbo-sacralis might be the result of abnormal stretching of the interarticular portions of the last lumbar vertebra, dependent upon imperfect ossification, originated with Königstein in 1871, and was based upon experiments similar to those of Robert, to which reference had already been made. At the same time, he admitted the possibility of Lambl's theory, and of the part played by an accessory vertebra. Von Weber-Ebenhof in 1874 described two cases, which he considered followed luxation of the lumbo-sacral articular processes, and contended that this was the general rule. Caries of the lumbo-sacral articular processes was considered by Didier in 1874, and by Herrgott in 1877, as a satisfactory explanation for the development of spondylolisthesis, and Van der Bosch expressed similar views in 1879.

In 1878 I contended that the cause of the olisthesis in the "kleines Wiener Becken" was to be found in a congenital anomaly of the sacrum, while in the "grosses Wiener Becken" the lesion in continuity in the interarticular portions of the last lumbar vertebra was due to fracture.

In 1882 Strasser believed that his case of lumbo-sacral olisthesis was the result of arthritis deformans of the lumbo-sacral joints, with the consecutive elongation of the arch of the last lumbar vertebra.

In the same year, appeared the highly important monograph of Neugebauer, in which he demonstrated that in lumbo-sacral spondylolisthesis only the anterior half of the last lumbar vertebra showed signs of displacement, and that the "dolicho-platy-kyrto-spondylus" which characterized it was the result of imperfect ossification of the interarticular portions of the last lumbar vertebra, or was due to their fracture. He accordingly defined spondylolisthesis as a mechanical deformity (Belastungs-difformität) of the last lumbar vertebra, developing gradually in extra-uterine life in the presence of certain predisposing conditions, as the result of the action of the body weight. Moreover, in 1852, Neugebauer stated on the basis of Strasser's case that an originally normal last lumbar vertebra might develop this deformity secondarily, as the result of an olisthesis due to fracture of the superior articular processes of the first sacral vertebra, should the former be arrested by the posterior margin of the first sacral vertebra and acquire an abnormal chronic inflammatory plasticity. Under such circumstances, a further olisthesis could develop only from the anterior half of the last lumbar vertebra.

Neugebauer reiterated similar views in 1883, 1884 and 1885, and laid particular stress upon the frequency of interarticular spondylolysis, which he gradually came to attribute more and more to a primary defect in development. In 1884 and 1885 Arbuthnot Lane dissented from Neugebauer's teaching concerning the great importance of congenital spondylolysis interarticularis, and contended that spondylolisthesis was merely a manifestation of a deformity of the last lumbar vertebra, due to excessive pressure resulting from the continued carrying of heavy burdens by the individual. This he held not only gave rise to the change in form of the vertebra, but also to the lesions in continuity in the interarticular portions.

Kruckenberg in 1885 pointed out that fracture of the lumbo-sacral articular processes might also occur secondarily in the course of an olisthesis; and H. von Meyer in 1877, after studying a case of spondylolisthesis of the first sacral vertebra, stated that the condition might occur as the result of imperfect development of the superior articular processes of the first sacral vertebra, even without the presence of spondylolysis interarticularis.

Neugebauer described a new spondylolisthetic pelvis in 1889, and demonstrated that it was certainly not attributable to hydrorrhachis, and clearly refuted the attacks of Lambl in that connection. In the following year he also adduced conclusive evidence of the possibility of a separation in continuity in the interarticular portion of the last lumbar vertebra occurring as the result of trauma, and gave a very accurate anatomical description of such a case.

In 1892 I attempted to bring together the various possible etiological factors concerned in the production of spondylolisthesis, and based my conclusions upon a careful study of the literature, the investigation of a comparatively large personal material, as well as upon experimental research. My investigations led me to define spondylolisthesis lumbo-sacralis as a gradual pushing forward of the last lumbar vertebra over the base of the sacrum, when the change might involve the vertebra *in toto* or only in its anterior half.

As a result of my studies, I held that any one of the following conditions might be considered *a priori* as etiological factors.

I. In olisthesis of the entire last lumbar vertebra.

1. Developmental anomalies of the lumbo-sacral articular processes.

2. Destruction by disease of the lumbo-sacral articular processes.
3. Fracture of the lumbo-sacral articular processes.
4. Luxation of the lumbo-sacral articular processes.

II. In olisthesis of the anterior half of the last lumbar vertebra.

1. Developmental anomalies of the arch of the last lumbar vertebra.
2. Softening or destruction by disease of the arch of the last lumbar vertebra.
3. Fracture of the arch of the last lumbar vertebra.
4. Changes in form resulting from carrying excessive burdens.

At that time I was able to adduce personal cases in support of the correctness of several of these hypotheses, more particularly for I, 1 and 3, and also for II, 1 and 3. As far as the others were concerned, I was obliged to state that they had been advanced merely as hypothetical or probable causes of the condition; as for example I, 4, but that their actual occurrence had not been demonstrated, nor did it appear likely that conclusive evidence in their support could be adduced in the future. Moreover, I was able to show in another specimen of pronounced spondylolisthesis lumbo-sacralis that it was impossible to determine which factors had been concerned in its production, when the synostosis at the displaced lumbo-sacral juncture was far advanced. Likewise it seemed important to me to point out that, even when the existence of one of the causal factors just mentioned could be demonstrated, it was necessary for excessive pressure on the part of the body weight to come into play in order for an olisthesis to develop from the predisposing etiological condition.

In 1892 Neugebauer reviewed the entire literature upon the subject, and considered all cases which had been either clinically or anatomically described up to that time. As a result, he stated that the important etiological factors were spondylolysis, which might be either congenital or the result of fracture, arthritis of the lumbo-sacral articular processes, and static deformation in the sense of Arbuthnot Lane. In the following year, he was able to enlarge his previous list by 8 additional clinical cases and 7 anatomical preparations, and he referred particularly to the highly interesting communication of Arbuthnot Lane in 1893, in which was described an attempt to cure spondylolisthesis, resulting from static deformation, by removing the spinous process and the arch of the fourth lumbar vertebra. This case is of particular interest as it represents the first attempt to treat spondylolisthesis by surgical measures.

During the following years a number of casuistical publications appeared, and I would mention especially the work of Williams, who, in 1899, described both anatomically and clinically, a well-marked case of spondylolisthesis occurring in a negress resulting from a spondylolysis interarticularis of traumatic origin, and which he stated was the sixth case which had been described in America up to that time. Moreover, I should like to call attention to the publication of Lawrence in 1900, who, after excluding the possibility of a lesion in continuity in the interarticular portions of the last lumbar vertebra being the etiological factor in his case, attributed it to imperfect development of the lumbo-sacral articular processes and of the arch of the last lumbar vertebra.

In 1900 Breus and Kolisko published their very thorough and systematic work upon spondylolisthesis, particularly from a pelikological point of view, to which I have already referred. Etiologically they considered that the typical factor in its production was spondylolysis interarticularis.

In 1905, I studied a new case of spondylolisthesis, in a 70-year-old woman, developing from congenital spondylolysis interarticularis of the last lumbar vertebra, and was able to demonstrate the presence of small accessory bones (Schalteknochen) in the space between the fragments of the left interarticular portion, just as I had repeatedly observed in simple congenital spondylolysis interarticularis without olisthesis. In 1901 Schwarte resuscitated the teachings of W. A. Freund, and contended that spondylolisthesis developing from congenital spondylolysis interarticularis was frequently due to the fact that the fœtal form of the pelvis had persisted, and consequently that the deformity was frequently of pelikogenous origin.

As the result of the many investigations concerning the etiology and pathogenesis of lumbo-sacral spondylolisthesis, I consider that it has been shown beyond peradventure that the etiological factor most frequently concerned is congenital spondylolysis articularis of the last lumbar vertebra. It has also been satisfactorily demonstrated that fracture of the interarticular portions of the last lumbar vertebra may sometime play a causal part, while occasionally, an unusually scanty development or fracture of the lumbo-sacral articular processes, as well as their involvement by arthritis, may be the predisposing cause.

When the lesion in continuity is limited to the interarticular portion of the last lumbar vertebra, only its anterior half glides forward, whereas the entire vertebra undergoes displacement in the other conditions. Moreover, when the vertebra becomes arrested in a certain location, the possibility must be considered that it may increase in length secondarily, in which event its body may later move further and further forward; just as we must admit that the flattening and lengthening of the interarticular portions of the last lumbar vertebra may be due to the action of undue pressure, as advocated by Arbuthnot Lane; but, personally, I consider it improbable that a marked olisthesis can develop in this manner. Spondylolisthesis occurring elsewhere than at the lumbo-sacral juncture is so very rare that it need not be considered at this time.

I believe that in the future our knowledge of spondylolisthesis will be advanced in great part by the study of pelves in which the anomaly is only slightly developed; as in them the etiological factors concerned can be much more clearly appreciated than in more advanced cases; since in the latter the presence of extensive synostoses may completely mask the underlying anatomical and etiological conditions. Such investigations will gradually place its etiology in a much clearer light, and will enable us to estimate more accurately

the frequency with which the various factors come into play. They will also have to take into consideration, to a much greater extent than previously, the part played by trauma in the development of spondylolysis, as well as by the mode of life of the individual. Finally, they will teach us whether spondylolisthesis really occurs so much more frequently in females than in males, as seems to be indicated by the statistics thus far available.

In order to solve these problems, it will be necessary to search directly and systematically for spondylolisthesis in all pathological anatomical material. At every autopsy, whether upon male or female subjects, the region of the lumbo-sacral juncture should be carefully examined, and, whenever it appears to be more prominent than usual, the pelvis should be removed and subjected to accurate preparation with a view of determining the existence of spondylolisthesis. Moreover, we should study all pelvic preparations, which are preserved in museums, with this point in mind.

In this manner I was enabled to discover three slight cases of spondylolisthesis lumbo-sacralis in my work in Prague prior to 1892, one of them being due to imperfect development of the lumbo-sacral articular processes, while in 1905 I described a fourth case. In about 4000 autopsies (25 per cent of which were upon children) performed under my supervision during the past four years in Strassburg, I discovered three additional examples of early spondylolisthesis. Etiologically they were quite ordinary, in so far as the causal factor was spondylolysis interarticularis; but on the other hand they were of especial interest in that they all occurred in males.

Up to 1893, out of a total of 115 cases, Neugebauer found only 7 examples of spondylolisthesis in males, an incidence of 6 per cent; Williams, in 1899, only 8 in 123 cases, 6.5 per cent; and, up to the time of this communication I could collect only 9 cases in 144, 6.2 per cent. If, however, I add to them the three cases to which I have just referred, we find 12 male cases in 147, and thus raise the incidence to 8.1 per cent. This being the case, it would appear permissible to predict that even in the male sex spondylolisthesis occurs much more frequently than is generally believed, and therefore the male pelvis must be examined with particular interest in this regard.

In this connection it is important to note that up to the present time all cases of spondylolisthesis occurring in males were only of slight degree, but whether this is due to the greater strength of the ligamentous structures and the more pronounced development of the musculature in that sex I am not yet prepared to state.

I shall now pass on to the description of my three new cases.

Case 1.—Museum specimen 6769 (Figs. 1 and 2). This specimen was obtained from a 70-year-old, very strongly built, peasant, 167 cm. in height, who died March 7, 1910, from embolism of the pulmonary artery. On removing the viscera from the abdominal cavity at autopsy, a marked protuberance was noted at the lumbo-sacral junction. Accordingly, after counting the normal number of cervical, dorsal and lumbar vertebræ, the pelvis was removed from the body and carefully prepared. On examination it was found that the spinous process of the 24th vertebra projected about 1 cm. further posteriorly than those of the other lumbar vertebræ, while its body was pushed forward to the same extent beyond the body of the 25th vertebra. A somewhat flattened exostosis 4 to 5 cm. broad extended from the anterior surface of the body of the 24th vertebra, principally to the left of the middle line, and was firmly united to a similarly formed exostosis of the superior border of the 25th vertebra by means of fibrous tissue. Moreover, a lip-like hyperostosis was present on the adjacent antero-lateral margins of the 24th and 25th vertebræ, while the intervertebral cartilage between them was markedly reduced in size.

On studying the relations of the 24th to the 25th vertebræ it was seen that the body of the former had advanced 1 cm. in front of the posterior border of the upper surface of the latter, and that both interarticular portions of the 24th vertebra presented a symmetrical spondylolysis interarticularis; the ends of the bone being smooth and about 1 cm. distant from one another, while the intervening space was filled by ligamentous structures, thus accounting for the increased length of the vertebra. The 25th vertebra presented signs of lumbo-sacral assimilation and was separated from the 26th by an intervertebral cartilage 8 mm. in thickness, while its alæ were only very slightly developed. On the right side, a suture separated the ala of the 25th from the normally developed ala of the 26th vertebra, while on the left side the two alæ were synostosed together; although a depression in the bone indicated their original union. Anteriorly and to the right, between the bodies of the 25th and 26th vertebræ, was a button-shaped exostosis, 4 cm. broad, 2 cm. long and 1.5 cm. high, which served to bind the two bones together. The spinous process of the 25th vertebra was split into a right and left half. The 26th vertebra was otherwise normal; as were also the 27th, 28th and 29th vertebræ. The 30th, however, appeared to be entirely assimilated to the sacrum and below it were three well-marked coccygeal vertebræ. Either side of the sacrum presented 5 sacral foramina, while the sacral hiatus gaped from the 28th vertebra downward. The sacro-iliac joints were not synostosed, and their anterior margins were lip-like. The inclination of the pelvis appeared somewhat less than normal and its bones were all strongly built and the acetabula were of moderate depth.

The pelvis presented the following measurements: Distance between iliac crests, 27.5; between anterior superior spines, 25.5; and between superior posterior spines, 8.5 cm. Superior strait: Conjugata vera, 10.5 cm.; transverse diameter, 12.5 cm.; right oblique, 12.5 cm.; left oblique, 12 cm.; right and left sacro-cotyloid diameters 8.2 and 7.8 cm., respectively. Plane of greatest pelvic dimensions: Conjugata, 13 cm. (extending to the junction between the 27th and 28th vertebræ); transverse diameter, 11 cm. Plane of least pelvic dimensions: Conjugata, 11.5 cm. (extending to the lower end of the 30th vertebra); distance between ischial spines, 9 cm.; distance between tubera ischii, 6.5 cm.

The sacral portion of the innominate bone was 8 cm. on each side (measured with a pelvimeter); the iliac portion was 6.4 cm. on the right and 5.5 cm. on the left side (tape measure), while the pubic portion measured 7.9 cm. on both sides. The sacrum measured 14 cm., from the upper margin of the 25th to the lower margin of the 30th vertebra, and 11.2 cm. in width.

From the study of this case, it appears that we have to do with a pelvis presenting a slight spondylolisthesis of the 24th vertebra resulting from an apparently congenital bilateral interarticular spondylolysis. This was combined with a lumbar assimilation of the 25th vertebra, and it is very interesting to note how this condition brought it about that the hypersynostotic processes, resulting from the olisthesis, involved not merely the junction between the 24th and 25th vertebræ, but also that between the 25th and 26th. The development of olisthesis in this case from the spondylolysis interarticularis may be explained by the hard labor which the man was obliged to perform, while further slipping

FIG. 1.

FIG. 2.

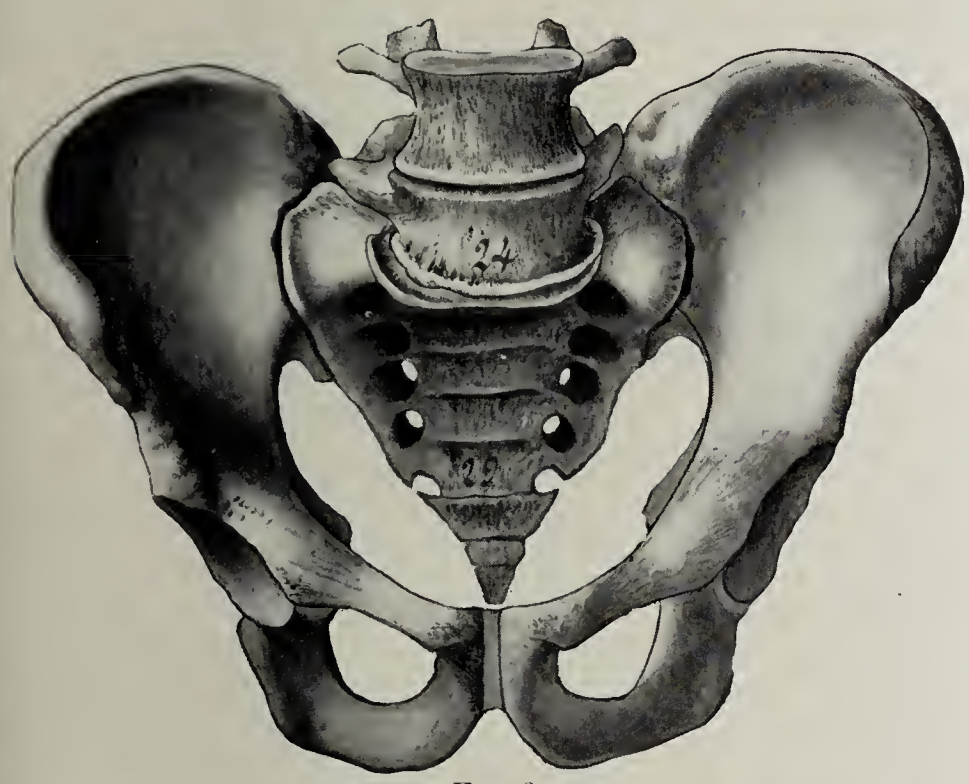

FIG. 3.

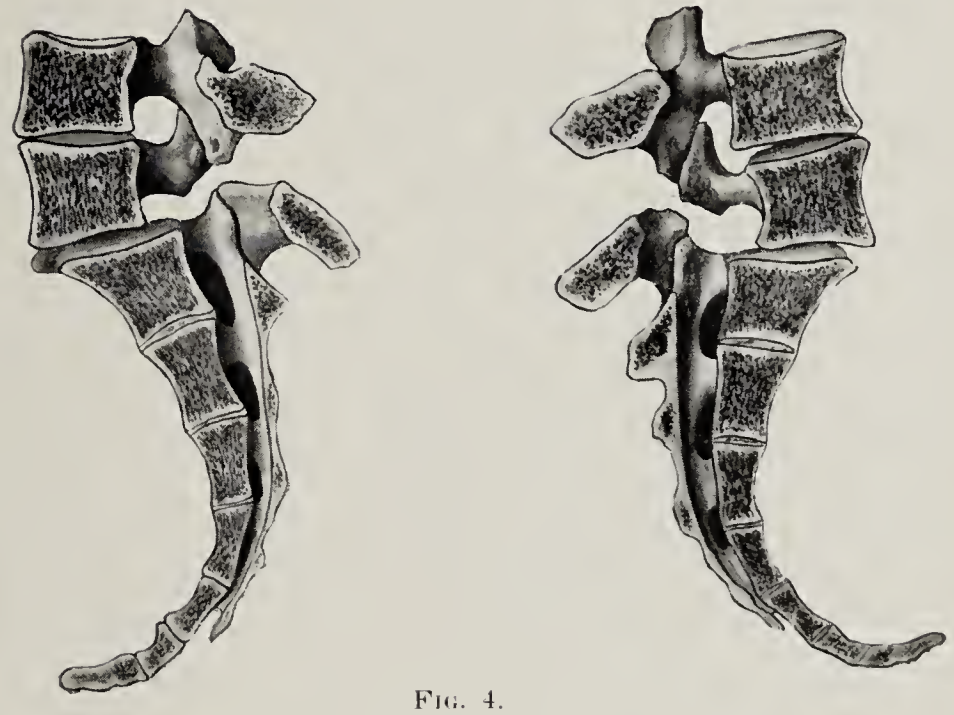

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIGS. 1 and 2.—Spondylolisthesis lumbo-sacralis e spondylolysi interart. cong. vert. lumb. V. Assimilatio lumbalis vert. sacr. I Strassburg. Mus. 6709. Male 70a.

FIGS. 3 and 4.—Spondylolisthesis lumbo-sacralis e spondylolysi interart. cong. vert. lumb. V. Strassburg. Mus. 6628. Male 55a.

FIGS. 5, 6, and 7.—Olisthesis vertebræ lumb. IV e spondylolysi interarticulari fracturosa. Strassburg. Mus. 6651. Male 55a.

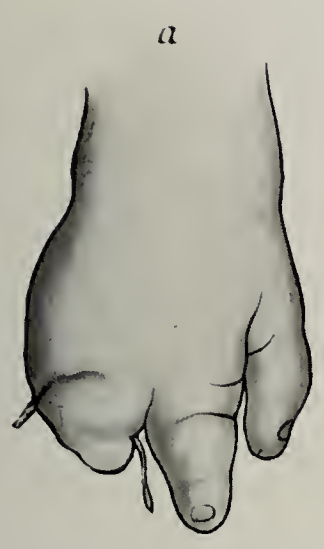

FIG. Ia.

FIG. Ib.

FIG. IIa.

FIG. IIb.

FIG. IV.

FIG. IIIb.

FIG. IIIa.

FIG. Ia, b.—Pero- et Syndactilia ligamentis amniotis effecta. Fœtus, 9 mens. Prag. Mus. 4943.
FIG. IIa, b.—Perodactylia ligamentis amniotis effecta. Female 70a. Prag. Mus. 5543.
FIG. III.—Ligamenta amniotica. Kind 3 hor. Prag. Mus. 5377.
FIG. IV.—Adhæsio amniotica interplacentam et caput fœtus papyracei. Prag. Mus. 5105.

FIG. VIII.

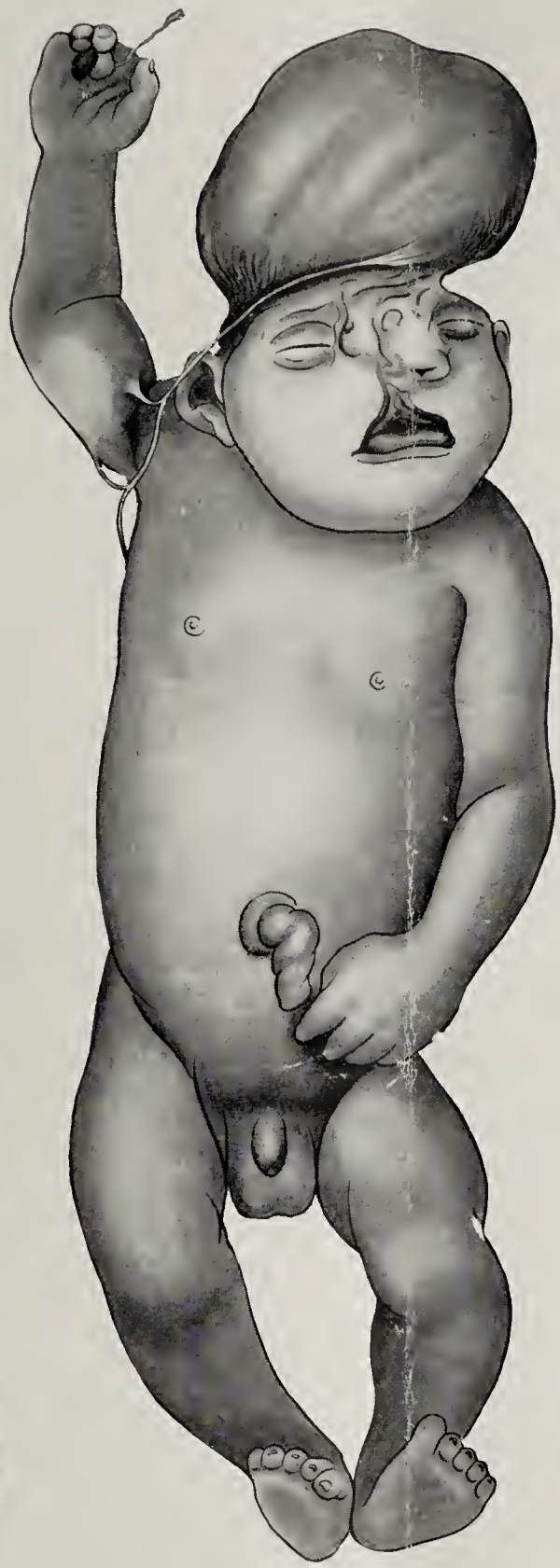

FIG. VI.

FIG. V.

FIG. VIIa.

FIG. VIIb.

FIG. V.—Schizosoma cum defecta extr. s. d. Fœtus, 38 cm. Prag. Mus. 5610.
FIG. VI.—Enkephalokele. Prosoposchisis. Ligamenta amniotica. Strassburg. Mus. 1922.
FIG. VIIa, b.—Schizosoma. Prosoposchisis. Ligamenta amniotica. Involucrum amnioticum thoracis. Prag. Mus. 5490.
FIG. VIII.—Perobrachia sin. prob. amnio effecta. Male, 4 mens. Prag. Mus. 2417.

of the bone was arrested by the development of secondary exostoses about the bodies of the vertebræ.

CASE II.—Museum preparation 6628 (Figs. 3 and 4). This pelvis was found in a 55-year-old laborer whose corpse was drawn out of the Rhine, May 23, 1909. The body was very strongly built. The lumbo-sacral junction was very prominent, particularly on the right side, while the normal number of vertebræ were present in the cervical, dorsal and lumbar regions. On either side, the sacrum presented four foramina and the first coccygeal vertebra (the 30th), was typically caudal in character.

On inspecting the pelvis from behind, it was seen that the spinous process of the fifth lumbar vertebra projected 1 cm. more posteriorily than the corresponding processes of the other lumbar vertebra. The continuity of the interarticular portions of the last lumbar vertebra was broken on either side, exactly midway between the upper and lower articular processes, and their rounded margins gaped to the extent of 1 cm. The body of the fifth lumbar had advanced to the same extent over the upper surface of the body of the first sacral vertebra. Following the olisthesis, hyperostoses had developed upon the anterior and inferior margin of the body of the fifth lumbar, as well as upon the anterior and superior margin of the body of the first sacral vertebra. The hyperostoses were 1 cm. high on the right side, but somewhat lower on the left, and a prolongation of the last intervertebral cartilage extended between them. The bodies of the several sacral vertebræ were fused together in the usual manner, and the sacral canal appeared to be closed as far as down the middle of the 28th vertebra. The pelvic inclination was very slightly diminished, while the bones of the pelvis appeared powerfully developed and free from any sign of injury.

Pelvic measurements: Distance between iliac crests 25.7 cm.; between anterior superior spines 23 cm. and between superior posterior spines 6.5 cm. The superior strait presented the following measurements: Conjugata vera, 10.2 cm.; transverse diameter, 12.7 cm.; right oblique, 12.2 cm.; left oblique, 12 cm.; right sacro-cotyloid, 7.6 cm., and left sacro cotyloid diameter 7 cm. Plane of greatest pelvic dimensions: Conjugata, 12 cm.; transverse, 11.3 cm. Plane of least pelvic dimensions: Conjugata, 11.8 cm.; distance between ischial spines, 10.2 cm. Pelvic outlet: Distance between tubera ischii, 11 cm. On either side, the sacral portion of the innominate bone measured 6.7 cm.; the iliac portion 6 cm., and the pubic portion 7 cm., while the sacrum was 12 cm. in length and 11 cm. in width.

In this instance the predisposing cause for the spondylolisthesis was exactly the same as in Case I, and we likewise had to do with an undoubtedly congenital spondylolysis interarticularis of either side of the fifth lumbar vertebra, from which the olisthesis gradually developed. At the time of death the olisthesis was only slightly developed, but it would in all probability have increased in extent had the individual lived; since, in the absence of the formation of synostoses, no mechanism existed to check further slipping.

CASE III.—Museum specimen 6651 (Figs. 5, 6 and 7). This pelvis was obtained from a 55-year-old peasant who committed suicide by hanging, August 9, 1909. The history gave no intimation of the existence of any abnormality on the part of the vertebral column, and the skeleton was tolerably strongly built. On removing the viscera at autopsy, it was noticed that the region between the fourth and fifth lumbar vertebræ was more prominent than usual, and also that the left transverse process of the fifth lumbar vertebra was very wide.

On more careful examination, it was found that a slight olisthesis, to the extent of 1 cm. had occurred, so that the body of the fourth lumbar vertebra projected over the anterior margin of the fifth. This was made possible by a spondylolysis in both interarticular portions of the fourth lumbar vertebra. The lower margin of this vertebra was drawn out in a lip-like manner, more particularly in its anterior portion, which was united by ligamentous structures with a similar lip-like hyperostosis, about 1 cm. thick, arising from the anterior and upper margin of the body of the fifth lumbar vertebra.

The separation in continuity in the interarticular portions of the fourth lumbar vertebra lay somewhat more posteriorily on the left than on the right side. On the right side it extended between the lower and middle third of the joint surface of the upper articular process, while on the left side it extended only through the lower end of the upper articular process. An irregularly bowed bony process extended from the upper articular process on the right side and grasped like a claw the corresponding interarticular portion. The two fragments of the vertebral arch of the fourth vertebra lay about 1 cm. apart and the intervening space was filled with ligamentous structures.

As compared with the spinous processes of the third, second and first lumbar vertebræ, that of the fourth vertebra was very prominent. The fifth lumbar vertebra presented no lesion in continuity in the interarticular portions, but the inferior margin of its body, like the upper margin of the first sacral vertebra was somewhat hyperostosed. The right transverse process of the former appeared normal, but on the left side there was a bony plate about 3 cm. in diameter and concave below, which was firmly united by ligamentous structures with a correspondingly formed protuberance arising from the upper surface of the left wing of the first sacral vertebra.

The sacrum was made up of six vertebræ of which the sixth was formed by the 30th vertebra, which was definitely assimilated to the sacrum, below which came three fused caudal vertebræ. On the left side of the 29th and 30th vertebræ there was an irregularly formed, jagged exostosis, while the entire left half of the former appeared to be irregularly hyperostosed. Four sacral foramina were present on either side. The ilio-sacral joints were open and their anterior margins somewhat hyperostosed. The pelvic inclination appeared normal. The descending ramus of the right pubic bone presented a fracture, which had healed with a perceptible hump, while the ascending ramus of the left ischium likewise presented a fracture, which had healed by hyperostosis.

Pelvic measurements: Distance between crests, 23.5 cm.; between anterior superior spines, 20.5 cm.; between superior posterior spines, 7 cm. Superior strait: Conjugata vera, 9.3 cm.; transverse diameter, 15.5 cm.; right oblique, 11.2; left oblique, 11.2 cm.; right sacro-cotyloid, 9 cm.; left sacro-cotyloid, 9 cm. Plane of greatest dimensions: Antero-posterior diameter, 11.5 cm.; transverse, 10.5 cm. Plane of least pelvic dimensions: Antero-posterio diameter, 11.5 cm.; distance between ischial spines, 8 cm. Pelvic outlet: Distance between tubera ischii, 8 cm. On either side, the sacral portions of the innominate bone measured 7.5 cm.; iliac portions, 6 cm., and pubic portions, 6 cm. The sacrum was 12 cm. in height and 11 cm. in width.

In this specimen, the olisthesis of the fourth lumbar vertebra was likewise the result of a spondylolysis interarticularis. Leaving out of consideration the fact that the olisthesis involved the fourth lumbar vertebra, I consider that the interesting feature of the case is the probability that the spondylolysis interarticularis could be attributed to a fracture. This would seem to be borne out by the irregular outline of the separation of the interarticular portions, which on the right side extended through the superior articular process itself, and in addition by the presence of undoubted traces of fracture on the anterior wall of the pelvis and the lower end of the sacrum. The hyperostosis of the left transverse process of the fifth lumbar vertebra, as well as that of the left ala of the first sacral vertebra might also have resulted from a fracture, but I consider it more likely that they are secondary processes resulting from the olisthesis.

Therefore, I believe that this man had sustained a fracture of

the pelvis, involving the arch of the fourth lumbar vertebra, from which the spondylolisthesis had gradually developed, while fixation had not occurred up to the time of his death. It is greatly to be regretted that a history of the case is entirely lacking.

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ON DIABETIC ACIDOSIS.*

By Prof. A. Magnus-Levy, Berlin.

What do we understand by the term acidosis, a name first employed by Naunyn? Acidosis means the *accumulation* of acids in the body, in sharp distinction to the *formation* of acids which are produced, indeed, in every moment of normal life. In the normal metabolism substances of acid or alkaline properties are continuously being formed, but the tendency of metabolism is towards their neutralization. Probably all acids, which we encounter in pathological states, are produced as intermediary products in the normal change of matter. We know this to be true of uric acid, of oxalic acid and of glycuronic acid, etc.; we may assume it of homogentisic acid, of oxybutyric acid and of others. We, therefore, are not justified in defining acidosis, simply as a formation or as an appearance of acids which do not occur in normal health.

The accumulation of acids, the essential character of acidosis, presupposes in each case a disturbance of oxidation. Whether, besides the disturbed oxidation an increased formation of acids is present in acidosis is another question, and must be answered separately in each single case. (If homogentisic acid is a regular intermediary product in the katabolism of phenylamine and tyrosine, as some authors believe, its quantity will depend merely on the amount of katabolized albumen. The alcaptonturic individual will not produce larger quantities of this acid than a healthy person, but in the normal individual total combustion of the intermediary products takes place, while in the alcaptonuric patient the acid is neither split up nor oxidized.)

Similarly with oxybutyric acid, the principal subject of my lecture, we must consider whether it is formed in a larger amount in diabetes than in normal life.

Besides these that I have mentioned, other acids occur as results of metabolism, such as lactic acid, volatile fatty acids, higher fatty acids, amygdalic acid and carbonic acid. Some among these display specific effects, even when present only in small quantity, as does uric acid, oxalic acid and perhaps the lower fatty acids. These specific effects do not come under the term of acidosis, which simply means the general result of acidification. This, indeed, takes place only when acids accumulate in very large quantities, such as are sufficient to disturb by their acid character the processes taking place in the organism. If we leave out of question the end product of all oxidation, carbonic acid, which has scarcely the character of an acid, only one acid remains, to which we may apply the name of acidosis in the above sense. This acid is the oxybutyric acid and dependent upon it diacetic acid. Whether besides this group another kind of acidosis occurs in pathology, namely, an acidosis produced by lactic acid, as yet seems doubtful.

You are all aware of the fact that oxybutyric acid undergoes oxidation into diacetic acid, and that from the latter acetone can be formed. It is hardly necessary to speak at length of the latter body, which has been the subject for intensive re-

* Paper read before the Johns Hopkins Hospital Medical Society, May 9, 1910.

search for many years. Two authors, Folin and Embden, found simultaneously that the acetone present in the urine is not eliminated as such at all, or only to a small part. It is a product of self-disintegration of the diacetic acid transferred by the kidneys from the blood into the urine. The acetone, too, which is exhaled by the lungs, is not present in the blood as such, but occurs in the form of diacetic acid.

Whenever tests for acetone are positive, we should consider diacetic acid to be present. The name acetonuria, still in use, may be used as synonymous with acidosis. The strong and characteristic smell of acetone in the expired air is an excellent guide for its diagnosis. With a subtle sense of smell one is able to observe the presence of acidosis and even to differentiate its intensity. In my experience the smell of acetone is observed in almost every tenth patient entering the hospital. I would like to emphasize here that acidosis is a very common occurrence. Acetone bodies, which is a comprehensive name for oxybutyric acid, diacetic acid and acetone, are temporarily formed in almost all diseases. Several, even numerous, forms of acidosis or, as one called it formerly, acetonuria, have been described. But all these forms are identical when considered from an etiological standpoint and are all to be classified under the same head. In general, acetone bodies are eliminated always when carbohydrates are lacking in the organism, or, when they are not utilized in a normal way. Under these conditions, indeed, the oxidation of protein and of fat will be deficient and oxybutyric acid will appear in the urine. Acidosis will occur *every time,* when from any reason, the taking of food and especially of starch and of sugar, sinks to a minimum.

This applies to all kinds of acetonuria—to the acetonuria from starvation or from exclusive animal food, to the acetonuria in fever, in gastro-enteritis and to the acidosis appearing in the latter stages of cancer. Only upon one point do we still remain in doubt, whether besides the absence of carbohydrate, there exist *other* circumstances, which, although they do not induce acidosis, yet may increase and modify it. Practically this question is rather irrelevant, and I think it an unnecessary discussion of the subject. Another question is of far greater importance, and that is the difference between diabetic and non-diabetic acidosis. Except in diabetes the elimination of acetone bodies rarely exceeds 10 or 15 grams, and when such quantities appear in urine, they do so only for a short time; in diabetes, on the contrary, the elimination may reach 30, 40 and more grams, and acidosis of this height may last for months and even for years. We know this fact since the early eighties, a period when we did not yet employ alkalies.

Here I would like to call your attention to the very important deduction, that a patient with severe diabetes, and with a very marked acidosis, may, under favorable circumstances, live for years without suffering *immediate* damage to his health. He is, it is true, according to Frerich's words, menaced by the danger of a certain and unexpected death, but this end may not be reached for many years. And this danger is imminent only in the *diabetic* patient, whose capacity for utilizing carbohydrates is extremely weakened. When the interest in acidosis became general among practitioners, when the Legal-Gerhardt test, so often positive, revealed the frequency of strong acetonuria in non-diabetic diseases, a feeling of apprehension arose. The bad prognosis which persistent and marked acidosis gives in diabetes was transferred without reason to acidosis existing in diseases other than diabetes. But acidosis never is a threatening danger in *such* patients. Acidosis as such has nothing to do with the symptoms and with the dangers of such diseases. The idea of the specialists in children's diseases was wrong, who, in studying the acidosis which occurs in the alimentary disturbances of nursing babies, ascribed the cachexia and death of the children to oxybutyric acid.

Furthermore, in diabetes acidosis, even when it has lasted for years, induces no *immediate* harmful consequences. Thus acidosis, which exists other than in this disease, being far weaker and of short duration, is without clinical interest and without prognostic value.

You are aware that the human organism, as well as that of carnivorous animals, defends itself against the action of accumulated acids by forming an alkaline body, ammonia. A diabetic patient at any time has at his disposal 6 or 8 grams of ammonia. The neutralization of acids by ammonia prevents deprivation of alkalies and a change in the alkalinity of the most important cells. With 6 or 8 grams of ammonia, 40 or 50 grams of oxybutyric acid can be eliminated month after month, without acidosis becoming deleterious. A *fatal acid-poisoning* will occur only then, when the accumulation of the acids reaches twice or three times these amounts. There is a difference between *acidosis,* spoken of in the common sense, and a *fatal* acid-poisoning, a difference which though only in the quantity of acids, yet cannot be emphasized strongly enough. Outside of diabetes, such an enormous rise of the accumulation of acid never takes place, so far as we know at present. The coma produced by it is limited to diabetes and merits the name of coma diabeticum.

Stadelmann, a pupil of Naunyn, was the first, as you well know, to consider diabetic coma to be a fatal acid poisoning. He compared it to the experimental poisoning by muriatic acid in experiments with animals. According to Walther's fine discovery, rabbits, after having been given 0.9 gram of HCl per kilo of body weight within 24 hours, die in a comatose state. The striking analogy between this form of acid poisoning and that of diabetic coma, emphasized by Stadelmann, exists in the similarity of the clinical symptoms, especially the changed and deepened breathing, further in the strongly diminished quantity of carbonic acid of the venous blood, together with the diminution of the alkalies as determined by titration. Aside from these symptoms the occurrence of ammonia in the urine is common also to both states. One link alone was missing in the chain of proofs furnished by Stadelmann. It had not yet been demonstrated that such an amount of acid, as was necessary to bring about the death of the rabbit, was present in a case of human diabetes. The *urine* of comatose diabetic subjects not only contained no larger amount of organic acid, but rather less than in the time pre-

ceding the coma. With one exception this quantity did not exceed 20 grams. That is the reason the theory of Stadelmann was doubted. The total quantity of acid found in any given case *appeared* insufficient.

A mistake had been made, however, in looking for their presence in the *urine* of deceased patients; it would have been just as much of an error to have looked for muriatic acid in the urine of dying rabbits. The lessened alkalinity of the kidneys diminishes the secretory power, the stream of urine decreases rapidly, sufficient elimination of the acid either ingested in an experiment, or formed within the body of a diabetic patient does not take place. Both the poisoned animal and the diabetic patient do *not* die from the acid which has been *eliminated* in a neutralized state, but from the acid which *remains in the body.* The presence of the acids was not to be looked for in the *urine,* but in the *organs* of the corpse. By laying stress upon this point of view I really have been able to find in the body by analysis of blood, liver, muscles, etc., quantities of 100 to 200 grams of oxybutyric acid. Calculated per kilogram and allowing for differences in molecular weight, these amounts are just as large, and even larger, than those which induced the death of Walther's rabbits.

In the urine also enormous quantities may be found, but only if the patient survives the comatose state, so that the elimination of acids takes place in a sufficient way. I was lucky enough to establish this fact in a boy under the care of my teacher, Naunyn. This boy, only 30 kilograms in weight, underwent a most severe coma, but was saved by the use of almost 200 grams of sodium bicarbonate in 24 hours. On this day the urine contained 160 grams of acetone bodies; the following days the elimination sank to a lower level.

In the experimental poisoning by acid, there exists an *experimentum crucis,* which proves the death to be really due to the action of the acid itself and not to secondary factors. If the acid circulating in the body is neutralized by intravenous injection of bicarbonate of soda, improvement follows immediately even when death seems to be imminent in the very next minutes. This *experimentum crucis* has succeeded also in diabetic coma, though only seldom, just as it was postulated by Stadelmann. I myself have seen three cases survive pronounced coma by use of bicarbonate of soda, two of them being children, one a patient of sixty years.

Here in America the doctrine of Stadelmann-Naunyn was well received and also it has been developed farther. In Germany, too, it has been acknowledged more than formerly since the new proofs have been furnished. According to my personal opinion, scarcely any other theory upon the entire field of metabolic science has better support and has been worked out more thoroughly both qualitatively and quantitatively. Yet it is proper that all objections which have arisen against it in the course of years should be considered carefully.

Four objections are to be named. The first one is the relative inefficiency of the alkaline treatment. It must be conceded that only few cases are known, in which an advanced diabetic coma has disappeared under the use of bicarbonate of soda, in contrast to the *absolute* efficiency of alkalies in the case of the rabbit. But it must not be forgotten that there is a marked difference between acid poisoning in experiments and in coma. In the first a certain limited and well-known amount of acid is introduced into the organism; when this quantity has been neutralized by the once-administered bicarbonate of soda, danger is over at once and will not reappear. During diabetic coma, on the other hand, the formation of acid does *not stop a moment;* new molecules enter continuously into the metabolism, to such a degree that the ingestion of bicarbonate of soda does not keep step. In order to neutralize 150 grams of oxybutyric acid, formed in the course of 24 hours, a quantity of 120 grams of bicarbonate of soda is required. Even when absorbed, the arrival of the alkali at the menaced centers of the brain and its utilization there is by no means to be taken for granted in every case. Only when the immense production of acids diminishes, or rather if oxidation takes place again—which, however, is not the case, as long as coma is at its height—will the alkalies ingested be sufficient to neutralize the acids. The urine then becomes alkaline and the diabetic patient will survive the coma. This quantitative calculation reveals why bicarbonate of soda therapy fails so often in advanced coma, but at the same time it is obvious that this failure does not contradict the theory of Stadelmann.

The second objection to be mentioned seems to be of more importance. It arose from the modern theories of acidity and alkalinity. Since acidity and alkalinity have been defined by the teachings of physical chemistry as the degree of concentration in hydrogen and hydroxyl ions, it has been pointed out that the fluids and the secretions of the body are fairly neutral, if measured with this measure, with the single exception of the gastric and pancreatic secretions. The amount of hydroxyl and hydrogen ions in the blood serum does not undergo marked variations either in the various conditions of normal life or in illness. Even in the acid-poisoning of rabbits only a slight derangement of the neutral point of the reaction occurs and a slight decrease in the alkalinity takes place. In diabetic coma, however, such a decrease has not been found. Silli and Benedict, who carried out these experiments, therefore, deny any analogy between diabetic coma and the experimental acid-poisoning. They deny that the former comes under the head of acid-poisoning.

But their argument does not hold good. Besides other objections, which could be made, the main difference lies in the fact that Benedict, unlike Walther, did not inject the muriatic acid into the *stomach* of the animals, but introduced it in the form of a continuous stream into the veins. The blood was mixed with the acid fluid directly, without the latter having been passed through the walls of the intestines, and the intravenous injection was continued until death. Under these circumstances the actual concentration of ions at the moment of death, of course, is higher than that, which would have been reached if the acid had entered slowly and evenly from the stomach into the blood. I think, if the acid-poisoning had been produced in the same manner, as in Walther's experiments, the alkalinity of the ions would have been the same as in diabetic coma; in other words, that here also the quantity

of hydroxyl ions would not have been distinctly diminished. Apart from these objections there is still another difference between experimental poisoning and diabetic coma. In the example of the rabbit the acid enters first the blood and only after that the cells; in the diabetic patient, on the contrary, the acids are actually produced in the cells themselves, and only a fraction of the total quantity enters the blood. Thus with the same degree of change of alkalinity in the nerve centers, upon which depends the death of the organism, the decrease of alkalinity of the blood will be greater in the animal than in the human patient. Death in both is not to be considered simply as a consequence of the changed reaction of the *blood,* but in reality as due to the poisoning of the *vital center,* by which in particular are meant especially the respiratory centers.

It is to be regretted, that we are still unable to measure the alkalinity of the *organs* themselves. But in spite of this lack we have complete evidence of the influence of acids upon what is taking place in the organism. I will give you a striking example from the field of normal metabolism. The production of even small quantities of lactic acid in the working muscles, and their entrance into the blood will excite the breathing center, although in this case, on account of the *small* amount of acids brought into play, no change in the ionic concentration in the blood occurs. This excitement of the respiratory centers is to be compared with the far stronger irritation occurring in coma. I will remind you also of the dreaded casts in the urine, which suddenly appear in many cases before the outbreak of the coma. I believe them to be acid casts, and I think that they indicate a local decrease of alkalinity in the kidneys, whilst the alkalinity of the blood and of the vital brain centers is yet normal.

To sum up the objections regarding the state of reaction in the organism I would say that alkalinity, in the sense of physical chemistry, and alkalinity in the common language of chemistry and of biology, are by no means identical. When there is no change in the ionic concentration, lessened alkalinity in the biological sense may be present and may be of greatest importance.

Two older objections to Stadelmann's theory are mentioned to-day more rarely than in former times, but even to these consideration must be paid. Sometimes a comatose state was encountered in diabetic patients, who did not show any signs of true acidosis. Neither the deepened breathing was present nor was the amount of carbonic acid in the blood diminished; the analysis of the urine failed to give oxybutyric acid. Upon closer observation of the clinical symptoms *these* comatose attacks have proved to be phenomena of a different order. A diabetic may die quite as well of uræmic coma or of epileptic coma, and even the weakness of the heart may be accompanied by a sort of coma. These forms of coma have nothing in common with the dyspnoic form of coma save unconsciousness. The critical eye of the clinician has little difficulty in recognizing them. Objections of this kind seldom are met with at present.

On the other hand, there have been observed symptoms of dyspneic coma in non-diabetic diseases. I have seen myself such a dyspneic coma only once and then in a uræmic patient;* but older authors of the eighties affirm that it was by no means exceptional in *urœmia* and in *fever*. Here also a diminution of carbonic acid in the blood and of the titrated alkali occurs similar to that in diabetes. Since the comatose state in nephritis and diabetes have at least two symptoms in common, must we consider that acid-poisoning is present also in uræmia? And is fatal acid-poisoning a symptom which is not specific for diabetes? Also in infectious diseases similar changes of the alkalinity are held to have been found. Of all the objections against the doctrine of Stadelmann, I believe *this one* to be the most important. A full contradiction and definite refutation of this objection—I own it frankly—is as yet not possible; no detailed description of the clinical symptoms is given in the older observations which have been published, and the method of measuring the alkalinity has generally been inadequate. No attention has been paid any more to such events for 20 years, and I myself, though highly interested in the subject, have not had occasion to make researches upon this point, either clinical or experimental. But I am inclined to believe that a certain kind of *weak* acidosis could be in play here too. It is conceivable that lactic acid may have accumulated within the body of uræmic or infected patients. New inquiries on this point are needed. It should also be determined, whether acids are stored up in the tissues of such patients in the same way as in diabetic coma. Although one should be cautious in predicting the results of future investigations, I will express my opinion that neither of these lines of research will reveal the existence of a true acidosis in nephritis, *fully* corresponding to diabetic acidosis. Even should an accumulation of lactic acid be found, there will be a difference in its intensity. Although certain symptoms of acidosis as lessened alkalinity of the blood and deepened breathing may be present, other and more important symptoms may be missed, and also with the first symptoms differences are to be found. I find a support for this opinion in an unpublished piece of work of Fraenkel, a pupil of Kraus. He demonstrated that in spite of a certain resemblance, the figures of alkalinity obtained either by titrimetric methods or by measuring the carbonic acid in uræmia and infectious diseases were by no means identical with those obtained in the diabetic coma.

Having thus discussed the clinical aspect of acidosis I turn towards the chemical problem.

The inquiries upon the chemical connections of the acetone bodies, performed during the last decade, have broadened our knowledge, not only regarding the special pathogenesis of diabetic acidosis, but even concerning the general problems of metabolism.

It has been well known for years that acetone and the allied acids do not originate from carbohydrates. In the old controversy, however, the first reliable proof as to whether pro-

* Having just returned from America I observed it for a second time in a uræmic patient, but this time on closer observation, its character struck me as being different from the dyspneic coma in diabetes.

tein or fat was the mother-substance of the acetone bodies, was given only then, when it became evident that in a single experiment the amount of metabolized protein did not suffice for the formation of oxybutyric acid. I found in a boy suffering from diabetic coma, during three days a sum total of 342 grams of acetone bodies in the urine, but during this space of time only 270 grams of albumen were decomposed, in other words a far smaller amount. From the protein large quantities of sugar had been formed; it was, therefore, obvious that the protein alone could not have furnished such immense quantities of organic acids in the same time. In this example at least a great part of the acetone bodies must have been derived from the fat. However, this fact did not contradict a simultaneous formation from protein. Further experiments, carried out by Schwarz, Embden and Baer, proved, indeed, that acetone bodies may originate from both protein and fat.

All the researches of these authors are based upon the principle of feeding—in the presence of acidosis—a certain substance and of observing its influence upon the output of acetone bodies. Previous experiments had given no clear results, because the unbroken molecule of protein or fat had been given. Schwarz on feeding butyric acid was the first to examine the influence of *intermediary* products of fat. Later on amino-acids, the components of the protein molecule, and different fatty acids which could be assumed to be intermediary products of the katabolism of fat were administered in such experiments. Such investigations were necessarily carried out, as I said before, when acidosis of a certain degree was present, that is upon diabetic patients or dogs, or upon healthy animals and men fed exclusively on animal food. However, as spontaneous variations occur frequently in acidosis, the results of such feeding experiments are somewhat doubtful. A discovery of Embden, therefore, was of great advantage in the study. Embden, as you know, found that the isolated dog's liver on artificial circulation produced diacetic acid, which was no doubt derived from the oxybutyric acid. The amount of acetone bodies transferred from the liver to the blood increased considerably when certain substances were added to the blood. This method of investigation, employed with great skilfulness by Embden, has proved its value by giving striking results. Both methods of inquiry, that on the liver and that on living diabetic subjects, supplement and control each other exceedingly well.

We learn from them the following facts: The immediate predecessor of oxybutyric acid is *butyric* acid, which, by oxidation in β position, is converted into its oxy-acid. Butyric acid has shown itself to be the strongest producer of acetone bodies. The reason is to be found in the fact that this conversion needs only a simple and slight chemical reaction, the addition of one atom of oxygen. The higher fatty acids, however, have to undergo far greater decomposition, a splitting off of many atoms of carbon, before they reach the stage of a chain with 4 C atoms. In feeding fatty acids, with from 4 to 10 atoms of C, it became manifest that capronic, caprinic and caprylic acids, all having an even number of carbon atoms yielded oxybutyric acid, while other acids with an uneven number of carbon atoms, such as propionic and valerianic acids, did not yield oxybutyric acid.

Inasmuch as true fatty acids with an uneven number of carbon atoms occur but rarely in the animal metabolism, or only in small quantities, the practical value of this demonstration is of no importance in the metabolic changes in diabetes. For biological chemistry, however, this discovery was of great moment. From it, in connection with other experiments, we have been enabled to conclude that the katabolism of fatty acids goes on by the loss of two carbon atoms from the original chain. The splitting off begins with an oxidation at the β carbon atom. Thus a β oxy- and further on a β keto-fatty acid is formed; finally the β C atom is found to be at the end of a new fatty acid in the shape of a carboxyl group. In this way from stearic acid very likely is formed palmitic acid, and from this an acid with 14, 12, 10 and 8 C atoms is derived, and then capronic and butyric acid.

In the same way as acid decomposition goes on by the loss of a chain of two carbon atoms, so the building up of fatty acids by synthesis seems to be accomplished by a gradual apposition of two combined carbon atoms. The formation of fat, or rather of fatty acids from sugar, which in the animal kingdom goes on in large proportions, has been explained in this way by Nencki, Hoppe-Seyler and myself, and Heath and others have found new supports for this theory.

The relations existing between amino-acids and acetone bodies are not so clearly known as with the fatty acids because the chemical processes are more complicated. Some of the amino-acids, leucine, tyrosine and phenylamine, seem to be katabolized to oxybutyric acid, while others, alanine, valine and glycocoll apparently are not, but appear, on the contrary, to diminish the output of acetone bodies. In studying these substances very interesting results have been obtained regarding the oxidative decomposition of the amino-acids which up to this time has been completely unknown.

However, I will forego a discussion of the purely chemical aspect of this question. For the present it is sufficient to state the principal result of these investigations, which is a well-marked antagonism between two groups of amino-acids. Protein is by no means to be considered as a unit, in so far as acidosis is concerned, because some of its components may *increase,* and others *decrease* acidosis. So, too, in the formation of sugar the two groups behave differently. It should be remarked that those amino-acids, which in the present state of our knowledge are convertible into sugar, do not yield oxybutyric acid, while on the other hand that group of amino-acids which undergo transformation into acetone bodies does not give any sugar. Since the protein molecule contains groups of different behavior regarding acidosis, it is clear why it failed to show obvious results in those experiments, in which the whole unsplit protein molecule was given.

Ten years ago I mentioned another possible way for the formation of oxybutyric acid. I thought that it might be formed in a synthetical way. This might take place by union

of two chains with two C atoms, but this way of formation has not yet been proven. Under this conception alcohol could furnish the material for the synthesis, but not only does it *not* increase the amount of acetone bodies in urine, but, on the contrary, it rather seems to diminish them.

Allow me to cast a retrospective glance at a period in which therapeutists have drawn erroneous conclusions from the results of these inquiries. When at the end of the last century only the fat, but not yet the protein, had been recognized as a source of acetone bodies, some physicians thought it necessary, to restrict the amount of fat taken by the diabetic, because they feared to raise the acidosis by giving fat. There are two errors in this deduction. The first is the wrong supposition, that increased *ingestion* of fat means increased *decomposition* of fat. But any one, possessing an elementary knowledge of the metabolism of matter and energy, knows that this is not the case. A surplus of fat given in the diet does not raise oxidation any more than does a higher amount of oxygen in the respired air. There is no danger that by *giving* more fat more fat will be decomposed, and more acetone bodies set free in the body. And even if this were true, a second factor was neglected, the factor of the destruction of the formed oxybutyric acid. Acidosis, and I repeat it again and again, does not only, or perhaps not at all, depend upon the *formation* of acids, but also and perhaps exclusively upon their combustion. Indeed after analyzing and taking into account the results of all experiments carried out in this direction, I may say, that the ingestion of fat in almost no case of diabetes has induced a marked increase in the output of acetone. An exception is given alone by butter, on account of its richness in glyceryls of butyric acid.

In opposition to the behavior of fat a higher intake of protein may sometimes increase acidosis. But this does not happen in a direct way, due to the formation of oxybutyric acid from protein, but in an indirect way. The demand made upon the katabolizing and oxidizing powers of the organism by large quantities of protein ingested, may lessen the oxidative powers which concern the combustion of acetone bodies. Such disturbances may arise also from other incidents such as troubles of the digestive tracts. Since fat does not *directly* increase acidosis, we should always try, not only to maintain the weight of the diabetic patient by a sufficient supply of fat in the diet, but even to increase the same.

The endeavor to avoid those food stuffs, which may *form* oxybutyric acid, is in vain, since protein and fat each do so. Alcohol and sugar—and the latter is not available by the diabetic patient—are the only material which do not yield acetone bodies. We ought rather to look for some substance which would diminish acidosis by increasing the splitting up and the combustion of the acetone bodies.

Numerous substances are known which do this, and they are included under the name of anti-ketonuric substances. The carbohydrates exert the strongest anti-ketonuric effect. From 50 to 80 grams of sugar are sufficient in a healthy man to dissipate a strong acidosis, induced by a starvation or by exclusive animal food. As yet we do not know how this effect is accomplished. Naunyn's explanation that the decomposition of the acetone bodies is due to the simultaneous combustion of carbohydrates by secondary oxidation is merely a paraphrase. We are, therefore, compelled to look upon the occurrence as a fact without explaining it. A like efficiency is due to the preformed carbohydrates of the food, and to those which are newly formed within the body from protein or other material. *Glycerine* owes its anti-ketonuric efficiency to its being transformed into sugar. In healthy men the decomposition of large quantities of albumen can dissipate acidosis. Its efficiency likewise is to be referred to the partial conversion into sugar. For those very amino-acids—alanine, glycocoll and aspartic acid, which in the experiment of Embden and Baer showed an anti-ketonuric effect—are the ones from which sugar is formed. However, glycerine and albumen, which in healthy persons diminish the quantity of acetone bodies, are as good as useless in severe diabetes.

This fact, which previously appeared surprising, is now understood. The sugar, formed from glycerine and from protein, whose combustion induced the combustion of acetone bodies in *healthy* persons, is eliminated in severe diabetes and thus cannot be utilized for the oxidation of the acetone bodies.

Most other materials, known to be anti-ketonuric, such as gluconic acid and others, are not food stuffs and, therefore, cannot be employed permanently. Alcohol, though in bad repute as a poisonous substance, is the only food stuff, which acts beneficially on the diabetic acidosis. It has been shown by experiments of Neubauer and of Benedict that it decreases materially the amount of acetone bodies in the urine. In coma I would not only consider the ingestion of alcohol to be allowed, but even to be desired. Therapeutic experiments with this substance in coma require great discretion because of the effect upon the patient and judgment in the interpretation of this effect. Besides alcohol no other compound of the food is at our disposal for combating acidosis. The difficulties of the struggle against acidosis depend upon the fact that the energy of sugar, the most powerful anti-ketonuric body, is not available in severe diabetes. Every improvement in the toleration for carbohydrates will be followed by a decrease in acidosis; but the general treatment of diabetes is outside of the limits of my lecture. You may attain your purpose of increasing sugar combustion and at the same time lessening acidosis by different means: you may restrict the quantity of protein in the food, you may prescribe fasting and vegetable days, you may give an oatmeal diet for two or three days, you may prescribe muscular exercise, or you may combine all these measures, and this will depend on the peculiarities of each individual case.

The use of bicarbonate of soda, which we continually employ in the treatment of severe acidosis, does not act directly against it; neither does it diminish the formation of acetone bodies, nor does it favor their combustion. In many cases, on the contrary, the amount of acetone bodies found in the urine

will increase, if great quantities of alkali are given. That by no means signifies a weakness of the oxidative powers, nor must it be considered as disadvantageous, or even dangerous. Rather the contrary is the case. While in general the amount of organic acids in the urine may be considered as an indicator of the degree of acidosis, this is different when alkalics are administered. Alkalies facilitate the elimination of acids by neutralizing them and thus withdraw the acids from oxidation; thus the amount of acids present in the body in a certain moment is diminished, and sufficient alkali is present always to neutralize them and to prevent poisonous action upon the cells. Naunyn contends that he has never seen a sudden death by coma following the withdrawal of carbohydrates since the time when he began to give sufficient quantities of alkalies from the beginning of a strict diet. But no matter how beneficial is the action of alkalies, we should not forget that they act only as a palliative remedy and that we should seek for more efficacious substances with which to combat directly the acidosis.

If that substance is once found, which will enable the diabetic to utilize carbohydrates, acidosis and its dangers will have disappeared.

I return to the problem which I touched slightly at the beginning of my lecture. I have mentioned the possibility that acidosis might have nothing to do with an increased formation of oxybutyric acid, but that it depended exclusively on disturbances of oxidation. One may imagine that also in normal life oxybutyric acid may be formed *to the same extent* as in the coma. This doctrine presupposes that each molecule of fatty acid and of amino-acid, which, according to our knowledge *may* be transformed into acetone bodies *must* really be so without exception. In other words, that this way of decomposition of fats and certain amino-acids, leading to oxybutyric acid, is not a facultative one, but that it is *obligatory*. I was able to prove that in diabetic coma such a maximum of oxybutyric acid was formed. One of my patients had decomposed 90 grams of protein and almost 200 grams of fat within 24 hours. From these substances, as far as calculation is possible to-day, about 110 grams of acetone bodies could be derived. This quantity really was found to be eliminated by the urine during three subsequent days. A healthy man living on a carbohydrate free diet would consume about 120 grams of albumen and 210 grams of fat daily; from these about 120 grams of oxybutyric acid could be formed; that means about $1\frac{1}{2}$ to 2 grams per kilo. Are we allowed to assume that he really forms such quantities of acids? We are allowed to do so if we can make it probable, that he is able to destroy them by combustion. Rabbits and dogs have oxidized 3 grams of this acid and even more per kilo introduced at one time into their stomachs. Since combustion is far easier when such substances are formed within the body, it might be possible for a healthy man to decompose 2 grams per kilo.

I furthermore call attention to the great amount of acetone bodies, which may be formed by non-diabetic organs. In Embden's experiments, the isolated dog's liver, an organ of scarcely 200 grams in weight, yielded 3, 4 and even 9 grams of diacetic acid, calculated for 24 hours. Since a part of it certainly had been destroyed, in the course of the experiment the production was in reality much larger.

No reasons exist in my opinion to disprove the conception that a healthy man may form and oxidize such large quantities of acetone bodies. For a long time these substances have been recognized as products of intermediary metabolism. According to my doctrine they would not be *facultative,* but they would be the *obligatory* products of the decomposition of fatty acids and of some amino-acids. If this doctrine is right, you see clearly that acidosis is *only* the consequence of disturbed oxidation. However, this conception is as yet not absolutely proven.

Embden takes the opposite standpoint. He observed that the surviving dog's liver, which was found to *produce* acetone bodies, was able also to *katabolize* diacetic acid. In continuing his researches on the liver of a depancreatized dog, he found that the destruction of diacetic acid was not smaller than with the liver of a healthy animal. Thus finding no decrease of oxidation, he considered acidosis to be caused by increased formation of acids. However, it is not allowable to transfer the results of the experiment upon a dog to the metabolism of man. Both behave differently. In living dogs accumulation of acids does not occur so generally and to the same intensity as in man, they do not lose the capacity for combustion of acetone bodies so completely as diabetic patients. There is a very marked difference between carnivorous and omnivorous animals. Men, using carbohydrates as food, destroy the oxybutyric acid, formed from fat and from albumen, *only* by the help of carbohydrates; they lose this capacity more or less if they become unable to katabolize the sugar molecule. Carnivorous animals, on the contrary, living on meat and fat, are enabled by nature to burn oxybutyric acid *without* the help of ingested carbohydrates. That means a wise arrangement of nature—and thus in diabetes of dogs accumulation of acids never reaches such an extent as in men.

You might ask me why accumulation of acids is increased so suddenly in diabetic coma. One may ascribe this sudden increase, at least in some cases, to a sudden decrease or even to a loss of the sugar combustion. Spitzer reports a case where this was obvious. Coma set in immediately after a strong physical shock combined with a psychical emotion. From that moment the elimination of sugar, up to then rather slight, rose to an abnormal height, and at the same time with increased loss of sugar the oxidation of acetone bodies was reduced to a minimum. Here no time was left for adaptation, which in the general course of diabetes prevents the rapid increase of acidosis. I might quote other examples where such a sudden increase of the toleration for sugar can be observed; I mean those very rare cases of acute diabetes, the beginning of which may sometimes be determined almost up to the hour by the sudden appearance of a terrible thirst in patients who until then showed not the slightest symptoms of diabetes. In such cases acidosis also arises suddenly and advances rapidly. The time being far advanced I confine myself to these few remarks.

It will not be quite easy to clear up all problems of this matter.

I am at the end of my lecture. I have not considered it my object to dwell upon those symptoms of acidosis which are considered more or less absolute facts. This was unnecessary with an audience so well informed on the subject as an audience of American physicians. I have undertaken the more valuable task to show, which problems are awaiting yet their answer and what objections may be raised to the doctrine of acidosis. To many of our profession the theme of acidosis seems to furnish no problems for future research. I hope to have demonstrated in which direction further research may be successful in order to advance both the theory of acidosis as well as its treatment.

SOME OBSERVATIONS ON THE BACTERIOLOGY OF THE BALTIMORE CITY WATER.*

By WILLIAM W. FORD, M. D.,

Associate Professor of Hygiene and Bacteriology, Johns Hopkins University.

The importance of a thorough knowledge of the water used by the city of Baltimore cannot be overestimated, especially at the present time when heavy expenditures are to be undertaken for the enlargement and permanent improvement of the supply. It is essential that the character of the water collected in the various water sheds which feed the city reservoirs should be well understood, particularly its content in bacteria, and the extent to which it is polluted by microörganisms derived from the intestinal tract. The results of such a study belong essentially to the medical public of the city, and if these results indicate a pollution of the supply which is at all likely to be a menace to the public health, it is the duty of every one conversant with the bacteriology of the city water to make his knowledge common knowledge. The number and character of the microörganisms found in the water delivered to the consumer will determine in a great measure the necessity of filtering it through sand filters, unless a careful examination of the various tributaries of the main streams utilized by the city should reveal that the pollution which may be found has its source in a few small streams which can be eliminated from the system.

During the past six years I have been making regular bacteriological examinations of the water drawn from the tap in the Bacteriological Laboratory, and in the organization of a class in Practical Hygiene have had the opportunity of paying frequent visits to the valley of the Gunpowder River and of studying several of its most important branches in Baltimore County, particularly the Beaver Dam Run, the Western Run, and the Oregon Branch. For a number of miles in the vicinity of these streams the general conditions prevalent along their banks have been carefully scrutinized, especially any local conditions which might favor a sewage contamination. The water from our tap has its source primarily in the Gunpowder River, and it has thus been possible to compare the bacteriological findings of the water as delivered with those of various samples collected from the river itself and from the above-mentioned tributaries. Recently it has seemed wise to review the work of this fairly long period of time and the results found during the different years agree so completely as to make deductions from the evidence presented of considerable value. The main conclusions obtained do not differ to any appreciable extent from those reached by Dr. W. R. Stokes and his co-workers in the Bacteriological Laboratory of the City Board of Health, but in a question so vital to the well-being of a community as its water supply, it is of paramount importance that the work done in different laboratories should be carefully compared. Only in this way can observations of permanent utility be made.

* Read before the Baltimore City Medical Society, May, 1910.

TAP WATER.

The water supplied to the Bacteriological Laboratory is derived from Guilford Lake and thus from the Gunpowder River at Lock Raven. This water has been examined at frequent intervals by the simplest methods in vogue for the study of water bacteria. The colonies have been counted on agar and gelatin plates, with 1 cc., 1/10 cc. and 1/100 cc. quantities. The average of these three counts has been taken to represent the bacterial content of the samples. Fermentation tubes of 1 per cent dextrose broth have been planted with 1 cc. and 1/10 cc. quantities and rarely with 1/100 cc. When these tubes showed positive fermentation by the production of acid and the evolution of gas, plates have been poured from the open bulb, the various colonies fished and planted on agar, and subcultures made in agar, gelatin, potato, Dunham's solution, litmus milk and various sugars. These reactions together with the morphology and motility of the organisms have served to establish the identification of the various species.

The number of organisms per cubic centimeter in our tap water is not large. It is uniformly below the standard of purity, 1000 to the cubic centimeter, and is usually between 500 and 600. It may be as low as 300 to the cubic centimeter. On rare occasions it may be increased to 1500 or even 2000. A high bacterial count is not common and is usually associated with heavy rains in the vicinity of Baltimore and is accompanied by a great increase in turbidity. From the bacterial count alone there is little or no evidence of pollution. Fermentation tubes, however, show almost invariably a positive presumptive test for *Bacillus coli*. This is practically always

given in 1 cc. quantities and it has proved a rare event, during six years of routine examinations, for this test to fail. Occasionally when a single Smith tube is planted with such a quantity, there is no active fermentation of the sugar as a result, but if half a dozen tubes be planted at the same time the majority always shows a positive presumptive test. Not infrequently the tubes planted with 1/10 cc. also give positive results and on very rare occasions I have seen acid and gas develop in the tubes planted with 1/100 cc. When plates are poured from the fermentation tubes and the various bacteria isolated which give rise to the splitting up of the sugar, considerable diversity is evident in the characteristics of the microörganisms encountered. The principal isolations, nevertheless, have certain cultural features which indicate that their source of origin lies in the intestinal contents. The species may be grouped about six main types.

Group I. Bacillus Coli Type.

In the majority of instances the microörganisms found in the fermentation tube conform to the classical type of *Bacillus coli.* They are small, sluggishly motile bacilli which produce a rather thick, moist, non-pigmented growth on agar, fail to liquefy gelatin, acidify and coagulate litmus milk without digestion of the casein, and ferment dextrose with acid production and the evolution of a gas composed of a mixture of hydrogen and carbon dioxide, with the formula $\frac{H}{CO} = \frac{3-4}{1}$. Many of the strains isolated produce indol abundantly, the reaction being brought out by the addition of nitrites to the mixture of sulphuric acid and a Dunham's solution culture, and in many instances the usual dirty brown growth on potato is also seen. Neither indol production nor abundant growth on potato have been considered essential in the identification of the organism, the previously mentioned reactions being regarded as diagnostic.

Group II. Bacillus Proteus Vulgaris Type.

Organisms of the "proteus vulgaris" type have been isolated on a number of occasions. In morphology they are not unlike *Bacillus coli,* but are somewhat longer and thinner. They have a rapid darting motility characteristic of this group. Their colonies on agar and gelatin have spreading, *leaf-like* edges and the lattter medium is rapidly liquefied. On the surface of slant agar the growth is spreading and in stab gelatin cultures liquefaction progresses rapidly in a transverse direction along the surface of the solid medium. The organisms ferment dextrose with a gas formula of $\frac{H}{CO_2} = \frac{3-4}{1}$, the hydrogen being in excess of the carbon dioxide. Milk is not firmly coagulated but shows a soft clot, the reaction remaining alkaline, and the litmus being completely reduced. The clot is slowly dissolved and the litmus milk is eventually converted into a glairy, dirty brown fluid in which no trace of curd is visible. If fresh litmus be added, the reaction is seen to be alkaline. Indol is seldom produced by these microörganisms. They belong clearly to the "proteus vulgaris" group.

Group III. Bacillus Cloacae Type.

Bacteria of the "cloaca" type have been encountered from time to time in the tap water. They have a morphology and motility like that of *Bacillus coli* and on the surface of agar they look not unlike this microörganism. They acidify and coagulate milk, and produce non-spreading colonies in agar and gelatin. The latter medium is liquefied and the precipitated casein in the milk tubes slowly digested. The organisms ferment dextrose actively, the gas produced showing an inverted formula, $\frac{H}{CO_2} = \frac{1}{3-4}$, the carbon dioxide being in excess of the hydrogen. They may or may not produce indol and in some instances their liquefaction of gelatin is extremely slow.

Group IV. Paratyphoid or Paracolon Type.

In a few samples we have isolated species which must be called "paratyphoid" or "paracolon" bacilli. They resemble *Bacillus coli* or *Bacillus typhosus* in morphology and motility, fail to liquefy gelatin, and ferment dextrose with the usual *Bacillus coli* gas formula, $\frac{H}{CO_2} = \frac{3-4}{1}$. In milk they produce a slight but transient acidity which gives place to an alkaline reaction after the lapse of four or five days. Their cultural characters place them clearly in the intermediate group.

Group V. Liquefying Organisms like Bacillus Coli.

Under this heading we have placed a number of cultures which represent a distinct type. The organisms have the greatest superficial resemblance to *Bacillus coli* in morphology, motility and growth on agar. In the dextrose fermentation tube they produce an acidity and evolve a gas which has the regular formula $\frac{H}{CO_2} = \frac{3-4}{1}$. On potato they grow in a dirty brown layer. They may or may not produce indol. While thus having many of the characters of *Bacillus coli* they are distinguished from it by their rapid liquefaction of gelatin. The liquefaction is funnel-shaped, proceeding out from the line of growth of the bacteria and not from above downward, as in the "proteus" and "cloacae" cultures. The colonies have no tendency to spread and are thus distinguished from *Bacillus proteus vulgaris,* while by their gas formula they are differentiated from *Bacillus cloacae.* The species is a distinct one, and I have found it on a number of occasions in the city water.

Group VI. Bacillus Faecalis Alkaligenes Type.

Many of the fermentation tubes which show the presence of the various organisms above mentioned give in addition colonies which develop into a non-fermenting organism of great importance. This is Petruschky's *Bacillus faccalis alkaligenes.* It has a motility and growth on agar like that of *Bacillus typhosus,* fails to liquefy gelatin, produces an alkaline reaction in milk, and in the fermentation tube grows only in the open bulb with the production of alkali. This organism occurs frequently in the city water and may be isolated both from the fermentation tubes and from agar plates.

SIGNIFICANCE.

While the microörganisms belonging to the above-mentioned types are accompanied, in our city water, by the usual water bacteria, spore-bearers, pigmented forms, etc., the latter are in the minority. The species usually encountered are the non-pigmented, non-spore-bearing, sugar-splitting bacteria, and it is important to consider what significance must be attached to their isolation. It seems to me that but one opinion can be expressed as to these findings. They indicate a permanent and serious pollution of the supply. The presence of *Bacillus coli* regularly in one cubic centimeter quantities is recognized by all sanitarians as evidence of sewage contamination and its occasional isolation from smaller quantities, 1/10 cc., is evidence that this contamination is extensive in character. The presence of these other strains is also, I believe, not without considerable signficance. In some instances, as with *Bacillus cloacae,* we are dealing with an organism which is characteristically found in sewage from which source it was first isolated by its discoverer, Jordan (1). In other cases we have organisms of the "proteus" type, which may and probably do exist in nature, but many years ago I (2) pointed out that this species is, next to *Bacillus coli,* the most commonly found species in the intestinal tract of man, and it is not impossible that its presence in the city water is due to fæcal pollution. Other organisms which have been isolated, those of the "paratyphoid" and "alkaligenes" type, are essentially intestinal in character. This is especially true of Petruschky's bacillus which is present in the alimentary canal in nearly every individual. Finally the organisms mentioned above as "liquefying organisms," like *Bacillus coli* have long been viewed with suspicion by bacteriologists. They are probably identical with the organisms described in the literature as "liquefying coli" a misnomer which Durham (3) especially has deplored. I have isolated them frequently here in Baltimore from sewage, from some of the tributaries of the city water, as well as from the tap water itself, and from polluted deep water wells. They are identical in cultural characters with a liquefying bacillus which I described from the intestines several years ago and the late Major James Carroll, of Washington, stated that these organisms were very common in various samples of water examined by him in Washington and believed to be contaminated. While their significance as an index of pollution is by no means certain, as Prescott and Winslow (4) point out in regard to intestinal bacteria which are not *Bacillus coli* yet their constant isolation from the city water, which is definitely polluted by *Bacillus coli,* is not without considerable interest.

SOURCE OF POLLUTION.

We thus see that the water drawn from the tap shows the evidence of serious pollution and since these results have been obtained now for a period of six years this pollution evidently has a permanent character. If we now ask its source it is difficult, if not impossible, to point to any one particular stream which is responsible for the contamination. My own observations relate only to the district in the immediate vicinity of the small town of Cockeysville and are concerned with three especial tributaries which empty into the Gunpowder River in this locality. These small streams are Beaver Dam Run which passes through Cockeysville, the Oregon Branch, and the Western Run. The water of these three runs is grossly polluted. This can be made out simply by an inspection of their banks where the sewage of numerous farm houses and of one or two small settlements can be seen making its way directly into the streams. As these small runs join the Gunpowder not very far above the dam at Warren the origin of the contamination of the Gunpowder water is not far to seek. The evidences of pollution which may be gained by naked eye inspection are amply substantiated by the bacteriological examination of the water collected from the various runs and of samples drawn from the Gunpowder itself. The number of organisms in the river and in the tributaries is fairly high, varying from 2,000 to 25,000 per cubic centimeter, and the fermentation tube reveals a very serious pollution. The presumptive test is frequently positive in great dilution, 1/100 or even 1/1000. The species cultivated from the agar plates and from the Smith tubes conform to the types isolated from the tap water. *Bacillus coli* is most frequent, but *Bacillus cloacae,* the liquefying organism like *Bacillus coli,* and *Bacillus faecalis alkaligines* are also found with some constancy. Some of these small streams indeed seem to carry nothing but a diluted sewage. The sedimentation in Lock Raven and in the various city reservoirs has served only to diminish the number of microörganisms. It has not altered the essential character of the bacteria, the species which survive and appear at the tap being practically identical in character with those found in the Gunpowder water above the Warren Dam before any considerable sedimentation has taken place.

REMEDY.

If our ideas as to the pollution of the Gunpowder River shall be substantiated by the work of other investigators, or if other sources of fæcal contamination shall be found, as for instance in Lake Roland and its tributaries, with the study of which Dr. W. R. Stokes has been engaged for some time, then the question naturally arises as to the means which must be adopted to remedy this evil and protect the citizens of Baltimore from the risk of water-borne infections. In my opinion the pollution of the Gunpowder River is too great and the sources of contamination too manifold to permit the adoption of hygienic measures which would be stringent enough to alter the character of the water permanently and make it safe for drinking purposes. Since the Gunpowder River offers the city the most convenient and most valuable source of supply, or at least may be used as the chief portion of our system, this water must in some way be made suitable for domestic use. There is evidently but one method of bringing this about. The water must be filtered, preferably through sand filters. Fortunately, this measure has already been adopted by the city, and it is a matter of supererogation at the present time to call attention to its necessity. Our bacteriological examina-

tions serve then more to testify to the wisdom of these patriotic officials, who for some time now have insisted upon the installation of some system of sand filtration for the purification of our water supply, than to call attention to some measure which it is impossible to carry out.

Even if it be claimed that filtration will not necessarily diminish our mortality from typhoid fever, the chief water-borne disease, we must remember that there is abundant evidence to show that the adoption of filtration plants has been followed by a diminution of the mortality from enteric fever in many cities. That this is not always the case seems to be true from the experience of the city of Washington. It may be pointed out, that this latter city forms an exception to the general rule, and that the typhoid fever was evidently not associated with a polluted water supply, but was due apparently to bad hygienic conditions in regard to the milk and food furnished the city. We believe, however, that our water supply is contaminated, and that it should be purified on general principles of good sanitation. If it diminishes the typhoid mortality, then we shall indeed be fortunate. But we do not know the source of *all* of our typhoid fever. Some may be water-borne and personally I am inclined to believe that much of it is associated with our polluted supply. But some may be milk-borne and some may be the result of a direct transmission of the typhoid bacillus from one individual to another. Any one who has examined, over any length of time, the milk sold in the little shops in the poorer sections of the city, where the bacterial count may reach 3 to 4 million to the cubic centimeter, must realize that the conditions which allow this great bacterial pollution will also allow a pollution of the milk by *Bacillus typhosus*. And any one who has read that valuable little contribution of Baetjer (5) on an epidemic of tyhoid fever in Baltimore County, where 17 cases of typhoid occurred in two houses, must feel that part of this disease in our midst is due to direct infection or to chronic bacillus carriers. Let us first provide Baltimore City with pure wholesome water and eliminate our polluted supply as a possible source of typhoid fever. We shall then be in a position to devote all of our energies to a further study of this malady, ascertain more accurately the origin of the disease and adopt those preventive measures which modern hygiene is teaching us are effective in controlling the spread of this most serious infection.

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A CASE OF CONGENITAL DEFORMITIES (PATENT DUCTUS BOTALLI; ABSENCE OF LEFT KIDNEY AND CHRONIC PERIPHERAL ŒDEMA).

By Charles R. Kingsley, M. D.,
Medical House Officer, Johns Hopkins Hospital.

(From the Medical Clinic of the Johns Hopkins Hospital and University.)

Jennie L., a white child, five months old, of Russian parentage, was admitted to the medical side of the Johns Hopkins Hospital, August 31, 1909. According to the mother, both parents had been well, with no history of tuberculosis or alcoholism on either side. The patient was the last of a family of eight children, all normal and healthy. There had been no miscarriages. The patient was born after a nine-months' pregnancy, during which the mother did her usual housework, but suffered no trauma. The presentation was breach, but the labor was easy. Soon after birth the mother noticed that the child's hands and feet were swollen and the tongue was too large for the mouth. No attention was paid to this since the child nursed well and grew, but the continuation of the deformities decided the mother to take the child to the hospital.

On admission to the ward the patient was found to be of average size for her age, 56 cm. long, and fairly well nourished, weighing 5675 gm. She appeared normally bright and intelligent, noticing people, surrounding objects, and moving about actively. The skin was soft and smooth, with no eruption anywhere. The head was held up fairly well and seemed normally formed, with a small anterior, and an almost entirely closed posterior, fontanelle. There was no brachycephaly with shortening of the anterio-posterior diameter and flattening of the occiput, the measurements being about normal for a child five months of age. A growth of fine black hair covered the head; the eyebrows and lashes were long. There was a peculiar bluish pallor of the face, but no cyanosis of the lips and finger tips. The neck presented an odd appearance due to two folds of redundant skin which ran from behind the ears to the shoulders, extending about 8 cm. in breadth when stretched. A slight prominence of the eyes was noticeable; ocular movements were normal with no strabismus or nystagmus. There was no epicanthus and the face was not that described as typical of a mongol. The pupils were equal, reacting normally; scleræ clear and conjunctivæ of good color. Large, thin, flabby ears protruded at right angles to the head. Hearing was absent on the left side, and a purulent

FACE: NOTE LARGE TONGUE AND EARS.

CUTANEOUS FOLDS—FROM BEHIND.

HANDS SHOWING PECULIAR FINGERS AND OEDEMA.

CUTANEOUS FOLD—SIDE VIEW.

FEET: NOTE PUFFY OEDEMA.

discharge was found in the left external meatus. Breathing was unobstructed and the nose normal looking. A huge tongue protruded through the lips to a level with the surrounding skin. There was no furrowing or enlargement of the papillæ, but the tongue was coated and indented by the upper and lower alveolar ridges. The saliva was swallowed. There was a highly vaulted palate and a large uvula but no abnormality of the tonsils and pharynx. The lips were not especially thick or protruding and there were no rhagades. No glandular enlargement was found. The thyroid could not be felt and there was no substernal dulness to suggest a thymus gland. The thorax was well formed, free from rickety rosary and Harrison's grooves. In the notch of the epigastrium the cardiac impulse was most forcible and on percussion the heart's dulness was normal in location and size. On auscultation there was an embryocardia and a sawing systolic murmur, following the first sound, well heard over the left chest. At the base the systolic murmur was especially loud and vibrating with a point of maximum intensity over the upper third of the sternum; both second sounds were clear. The pulse was regular, of good quality, and well felt in the extremities. The abdomen looked natural, without marked prominence or hernia. A soft liver edge could be felt about 2 cm. below the costal margin. The spleen was not palpable. The genitalia were normal in all respects.

The extremities were bulbous, showing considerable swelling of the lower parts of the legs and forearms. The skin looked waxy and bluish over the dorsa of the hands and feet, pitting readily on pressure, but not thickened or indurated. The extremities were cold. The fingers and toes were long, showing a fusiform enlargement of the two proximal phalanges which were in slight flexion, the distal phalanx being in slight extension. A transverse line of constriction formed a groove at the terminal phalangeal joints, most marked in the fingers, but present in the toes to a lesser degree. Both finger and toe nails were growing almost at right angles to the digits, apparently pushed up by an overgrowth of the terminal phalangeal tissue. The muscular power and sensations seemed normal.

Examination of the blood showed a red cell count of 4,900,000, white cells 10,000, and hæmoglobin 78 per cent. The urine and fæces were normal. A Wassermann test, done on the blood serum, gave a negative result. X-ray plates of the hands showed no abnormality.

The child was kept on graded doses of thyroid extract in the belief that the condition might be an atypical form of cretinism, but after two months, there being no improvement, the drug was discontinued. Small doses of diuretic drugs combined with digitalis failed to affect the œdema. The tongue remained as on admission, large and protruding. The greatest difficulty was encountered in finding a modified milk suitable to the child's delicate digestive organs. There were several gastrointestinal upsets with vomiting, diarrhœa and a temperature of 101° F. The weight remained about as on admission with occasional fluctuations. The temperature, aside from the gastric upsets, was normal or slightly below; the pulse rate was normal. In January the child seemed weak and feeble, and on the 9th of the month her temperature rose suddenly, with a profuse diarrhœa and vomiting. There was no improvement in the condition and exitus occurred next day.

Autopsy (Dr. Whipple).—The interesting points in the autopsy findings are as follows: a very inconspicuous thymus, there being practically no tissue where the gland should be. Normal heart valves, but an open ductus Botalli, measuring about one millimeter in diameter. An acute diffuse cellular myocarditis. No special hypertrophy of the ventricles. Scattered areas of broncho-pneumonia in both lungs. The left ureter appeared normal at its entrance into the bladder and as far as followed up to the brim of the pelvis. Here it was lost and no remnant of kidney tissue was found in this area. The left adrenal was close to the diaphragm and appeared normal. The right kidney was very large, about the size of two normal kidneys. There was a single distorted pelvis coming from the anterior median portion of the irregular kidney mass, the long axis being nearly parallel with that of the vertebral column and lying almost completely to the right of the vena cava, which crossed over its mesial surface. The kidney substance looked in no way abnormal. An acute enteritis throughout the ileum was found.

The thyroid was small, pale, and uniform on section. The bone marrow appeared normal. Unfortunately, no permission to examine the brain could be obtained.

TRANSVERSE FRACTURE OF THE BODY OF THE ISCHIUM IN 1893; TERMINAL DISPLACEMENT IN 1902; DIAGNOSTICATED IN 1909.

By NORVELLE WALLACE SHARPE, M. D.,
St. Louis, Mo., U. S. A.

The case herewith detailed is not classified as unique, but of extreme rarity and interest.

Fractures of the ischium, participating in a general pelvic crush, are not notably rare.

Fractures of the ischium, without coincident pelvic fractures or complications are considerably more infrequent, and are worthy of record.

Fractures of the *body* of the ischium, the result of direct impact, and without coincident pelvic fractures or complications, producing but moderate disability and remaining undiscovered for an extended period of time, are not only noteworthy on account of interest and rarity, but specially merit consideration in conditions which involve a differential diagnosis.

The following dicta from *Scudder, Keen,* and *Stimson* are recorded as suggestive:

Scudder, "Treatment of Fractures," 1910; "fractures of sacrum, coccyx, symphysis pubis and ischium are extremely rare."

Keen, "Keen's Surgery," Vol. II, 1907; "fractures of the ischium, sacrum, and coccyx . . . . are very rare."

Stimson, "Fractures and Dislocations," 1907; "fracture of the ischium is one of the rarest of fractures of the pelvis. *Malgaigne* collected only six cases and his list has not been since increased by any reported in detail. In some of the cases almost the entire ischium was broken off, in others only the tuberosity. Experiment indicates that a fracture may pass into the cotyloid cavity. In three of Malgaigne's cases the cause was a fall upon the buttocks; the fourth a gunshot fracture, the fifth caused by an explosion, the sixth due to forceps manipulation, in a case formerly with the pelvic ring fractured, and ischium was broken. In the simple cases there was little or no displacement; in the gunshot fracture the fragment was displaced downward more than 2 inches by contraction of ham-string muscles, the displacement persisted but does not appear to have interfered materially with the movements of the limb."

Transverse fracture of body of right ischium (about ¼ size of original plate). Note ¾″ overlap of the caudad fragment (*cf.* Section 2 of Dr. Carman's report).

H. D. B., aet. 64, has led an active mercantile life, relieved by field and water sports abundant in quantity and choice in character. The patient is vigorous and well muscled, 5 feet 5 inches in height, weight 165 pounds, he exhibits a substantial amount of adipose. For some years has "had trouble with right leg"; an attack of left "sciatica" in 1901, and more or less so-called "sciatic pains" on both sides since. Right hip and thigh became troublesome in 1903; "could not keep up in my shooting"; "friends noted a slight drag," etc. Pains now began in hip, back, knee and foot, rarely at night, but more or less constant when walking; this pain and "consciousness of having a hip" have thus existed *seven years.* Patient has consulted numerous physicians both in the States and abroad, the various diagnoses leaning to some form of sciatic involvement. In 1909 an X-ray examination was made at a New York up-state sanitarium, and a diagnosis of "trochanter split and piece off of one side," rendered.

For the aforesaid "sciatica" relief has been sought through applications of electricity, liniments, Swedish movements, massage, "light treatment," leucodescent lamps, etc., but all without avail.

The trouble, not disabling, but ever present, remained without improvement, indeed it grew worse.

His condition was brought to my attention last November (1909); before any examination was made, he was referred to Carman (St. Louis) for a searching X-ray exploration. A diagnosis of fracture of right ischium was returned. At a later consultation (April 29, 1910), an effort was made to discover an anamnesic clue that would indicate when the fracture had occurred and how it had remained so successfully undiscovered.

Key to Plate.—Contrast sharp angulation at *a* (caused by cephalad displacement of caudad fragment) with normal graceful periphery of obturator foramen.

Patient's record shows that in 1897 he sustained a severe fall on a marble floor; a critical orientation of the facts coincident with and sequent to this accident leads to the conclusion that in no manner should it be considered the cause of the fracture. An antecedent accident proved more promising; in truth *the only casualty in the record that warrants serious consideration.* The details are:

In 1893, while fishing, patient sustained a severe fall, striking his right buttock on "a pointed rock" (in shape, I take it, akin to a cypress knee, familiar to those who shoot

or fish in the swamp and overflow lands of the South); there immediately followed intense local pain (patient states that he "was almost paralyzed"), this remained for several hours, but by the following morning merely the ordinary sensations of a severe contusion were present. No essential disability followed, and though moderate discomfort was more or less constantly in evidence he continued an active life, including his shooting and fishing. For this discomfort, during the succeeding years, he was subjected to the various forms of treatment above noted.

In 1902 while indulging in some "physical culture" exercises (ordered for the existing trouble), during which the right leg was extended and the thigh flexed sharply on the abdomen, *"something snapped"* within the right pelvis. This sensation was distinctly experienced by the patient, and beyond peradventure, his memory in this regard being quickened by the fact that he recalls having announced to a relative that as a result of this incident, he was "done with physical culture" and allied forms of treatment.

In 1903 hip and thigh became more troublesome, he could not maintain his former speed and endurance in a day's shoot, and his disability became patent to his friends (as noted above).

Most careful questioning fails either to shake the evidence just recorded or to introduce any other accident that might with reasonable probability be held to have definite etiologic significance.

The conclusion is therefore compelled that this ischium was fractured in 1893, and remained *undiscovered for sixteen years*. i. e., up to November, 1909.

The interesting question arises, is it not possible, during the energetic movements of the "physical culture" episode of 1902, that the overriding of the caudad fragment (see X-ray photograph) was developed; and that antedating said episode (i. e., 1893-1902) the fragments had remained in fair terminal apposition, maintained either by a reasonably intact periosteal bridge or an elastic fibrous bond, competent for all ordinary demands, but which yielded to the sudden violence of 1902 with consequent overriding. Furthermore, is it not probable that this overlapping displacement, once established in 1902 has continued, without reduction, to the present day?

It is remarkable that in a man, very intelligent, capable of giving a lucid description of facts and symptoms, anxious to maintain himself in the pink of condition, comfortably well-to-do, and under the observation of numerous physicians; it is indeed remarkable that such a fracture should remain *undiscovered for sixteen years*. There are two possible explanations: first, X-ray orientation had not been developed to its present accuracy in the earlier years of his disability, and as a result was neither frequently recommended nor often employed; second, the combination of a well-to-do patient, exceedingly solicitous regarding his physical condition, presenting a syndrome readily assignable to "sciatica" with no strikingly exceptional or highly suggestive clue leading toward an exhaustive examination and a more exact diagnosis—this combination probably proved the pit into which "all fell." It is stated that at no time during these many years was a rectal examination made.

Obviously: *Haec fabula docet rationem examinem sine cura culpam gravem esse.*

Present Condition.—Pain is moderate when seated or in bed, but constant when walking, it is accentuated during damp or unsettled weather. He uses a stick, and evidently "nurses" the right leg during locomotion, for excursion of the knee is automatically limited. States that he is liable to stumble over small obstacles; the resulting "jars" are painful, radiating down the thigh. Can definitely identify (and claims to have always been able to definitely identify) a relatively sensitive area, i. e., the tuberosity of the right ischium and peri-ischial structures. He continues to engage in a fairly active life but, handicapped as above, has eliminated the more vigorous forms of his customary sports.

Comparative measurements show relative dextral symptosis:

	Right.	Left.
Circumference calf	14″	14¼″
Circumference thigh lower ⅓	15¾″	17″
Circumference thigh middle ⅓	20⅛″	21¼″
Mid. symphysis to postmesial line	18″	21″
Ant. Sup. Spine Ilium to Internal Malleolus.	31½″	31¾″

The mid-symphysis postmesial measurement is particularly interesting in that it records dextral gluteal change.

Rectal examination reveals an area of the right ischium sensitive to pressure. This area exhibits a moderate entad boss, which accurately corresponds to the overlap of the caudad fragment of the ischium (see X-ray photograph).

Dr. Carman, to whom full credit must be accorded for supplying the correct X-ray diagnosis, in his report calls attention to—

1. A spear-like exostosis springing from the superior edge of the acetabulum; furthermore the articulation outline is indistinct.

2. There is fully a ¾-inch overlap (original plate practically life-size); the caudad fragment seen partly through the acetabulum, partly through the femoral head, being shown mesad to that extent.

3. If patient had not been so stout, a series of perspective views might have been obtained that would have afforded data regarding character of displacement and union.

Based upon Section 1 of Carman's report it would seem to be evident that a moderate hypertrophic arthritis is present. It is entirely conceivable that a portion of the gluteo-femoral syndrome is due to exacerbations of this condition.

Technically, it is entirely possible that pressure pains might be largely, if not wholly, relieved in such a condition by an attack directed toward the overlapping fragments.

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PERI-TONSILLAR ABSCESS.

By Mactier Warfield, M. D.,
Instructor in Laryngology, Johns Hopkins University.

This abscess is always painful, and at times dangerous. The laryngologist rarely sees one outside of a hospital, for the great majority of them come to the general practitioner, who either treats them after the method generally given in the text-books, a method often unsuccessful, and always dangerous, or frightened by its dangers and mindful of past failures, bears with resignation the sufferings of his patient until the abscess opens of itself. My excuse for this paper is that I wish to present a method of opening these abscesses, one which I have used for some time, that has never failed me, and which I believe to be perfectly safe, hoping that others may try it, in order that we may arrive at a correct judgment as to its value.

By a peri-tonsillar abscess, I mean one which is the result of an infection of the loose connective tissue immediately about the tonsil which presents the symptoms with which we are familiar as belonging to quinsy. Since it is supposed that the starting point of the infection may be anywhere in the peri-tonsillar connective tissue, the resulting abscess has no definite position where we may always look to find it. As it is also accompanied by great swelling and œdema of the mucous membrane over it, the area over which we can get fluctuations is therefore increased, and as the mouth can barely be opened, and hardly anything can be seen of the throat, it becomes impossible to definitely locate the abscess and find its point of greatest fluctuation. Examination by the finger affords the most accurate information, but this gives so much pain that few patients will submit to it.

In opening an abscess the procedure usually given in the text-books is this: when in any particular case an incision is decided upon, it is not attempted, as a rule, to definitely locate the abscess, but the incision is made at a site which experience has shown to be the usual point of greatest swelling, and where pus can be found. This incision is begun at a point opposite the junction of the uvula with the soft palate and about three-eighths of an inch external to the inner border of the anterior pillar of the fauces, and is carried from above downwards about one-third the distance from the point of origin to the lower border of the tonsil. The knife is wrapped to within a half inch of the point, and is plunged into the swelling to the depth of half an inch, care being taken not to wound the tongue on withdrawing it. Often when there have been unmistakable evidences of the presence of pus, and when the incision has been carefully made, the abscess is not opened.

There is hardly anything which occasions the physician greater chagrin than a failure of this kind, or does more to lower his reputation with his patient, who has had his pain increased instead of receiving the promised relief from suffering, and who now considers the doctor the cause of all his troubles. This incision is not without danger. In making it the ascending pharyngeal artery has been cut and the carotid also. Bosworth says that he never opens a peri-tonsillar abscess without a certain feeling of nervousness on that account.

To permit the abscess to open spontaneously has also its dangers. Abscesses have burst in sleep, and the pus entering the air-passages has drowned the patient. Pus has burrowed down, and found a way out in the axilla, or entering the pleural cavity has caused death. Most abscesses, when let alone, open of themselves between the fifth and tenth day, but at times this does not happen for five or six weeks, and by that time the patient is reduced to a pitiable condition from pain and want of food and sleep. Sometimes, either through fear of accident, or because of former failures, the patient or his family will not allow the abscess to be opened.

In a long service in the throat clinic of the Johns Hopkins Hospital, it has been possible for me to see a large number of peri-tonsillar abscesses, and to make observations which have led me to hold opinions as to their origin, and the best way of opening them, which differ from those usually held.

In the first place, instead of considering that the infection may enter, and the abscess arise at any point in the peri-tonsillar connective tissue, it seems quite evident that it always starts from the same point, and that point is in the supra-tonsillar fossa, and that the abscess is always the result of the extension of the infection to a cavity which opens into this fossa. This cavity or space is in the connective tissue, and extends outward along the superior border of the tonsil, and downward along its outer border, thus bounding it on two sides. The abscess begins at the supra-tonsillar fossa, and as pus continues to be formed it occupies first that part of the cavity which is above the tonsil and then the part on its outer border. As the part on the outer border of the tonsil becomes distended with pus, it forces the tonsil out of its usual position, and pushes it inward over towards the uvula, making it appear as if it were swollen itself, but its increase in size is only apparent and not real, for the abscess is never within the tonsil, but external to it.

The chief causes of peri-tonsillar abscesses are acute follicular tonsillitis, imperfectly removed tonsils and rheumatism. After an attack of acute tonsillitis, the pain and fever usually disappear at the end of three or four days, and the patient thinks he is getting well. But it is often only the lull before the storm. At the end of twenty-four or thirty-six hours, he feels a sudden sharp, stabbing pain in one tonsil, and that is the beginning of the abscess. The swollen tonsil has carried an inflamed crypt into the supra-tonsillar fossa, and infected it. Or the fossa may be infected by the small chronic abscesses which are the result of leaving parts of tonsillar crypts behind in removing a tonsil.

The abscess which is the result of the acute rheumatic

infection, starts as a small, circumscribed, deeply inflamed area over the supra-tonsillar fossa and the adjacent anterior pillar. It can be aborted if seen very early by the use of salicylate of soda.

Whatever the cause of the abscess may be and whether it is large or small, it can always be located in the supra-tonsillar fossa, which itself can easily be found even where the throat is very much swollen and distorted. This then is the place where the abscess is to be opened in every case.

The necessary incision is made with a curved bistoury, which is held parallel to the soft palate, with the edge of the blade looking forward, the back towards the posterior pillar, and the point directed outward towards the ear. The point is entered in the supra-tonsillar fossa, in the angle between the pillars of the fauces as high up as possible, and is passed outward until it meets with an elastic resistance, which is the abscess. This is entered, and the knife is brought out straight forward through the anterior pillar. As a rule the knife does not have to enter more than a half inch to reach the abscess. The cut in the anterior pillar is through swollen mucous membrane and does no harm. A bent probe can then be passed through the opening made in the abscess, over the tonsil and to its outer side, thus demonstrating the existence of the cavity there. As the ascending pharyngeal artery and the carotid are at the back of the knife, they are in no danger of being cut.

This incision, then, has these advantages: it is perfectly safe, it is easily made, and it is always successful.

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NOTES ON NEW BOOKS.

Symptomatic and Regional Therapeutics. By GEORGE HOWARD HOXIE, A. M., M. D. (*New York and London: D. Appleton & Co., 1910.*)

The title of this work excites curiosity as to its exact scope for as a rule it is not wise for too much attention to be directed to the treatment of symptoms. The temptation—too frequently succumbed to—is to give care rather to the relief of symptoms than to getting at their cause. Obviously in some cases we cannot do anything more than treat symptoms, as in hopeless cases of malignant diseases. In some cases special attention to a particular symptom is important and such a section as is here given on the treatment of itching is excellent, but to treat emaciation as a symptom hardly seems very good therapeutics. The reasons are not evident for placing some conditions under certain headings. Thus it is difficult to see why the serum treatment of diphtheria should be discussed under the heading of "chronic inflammations." Even "regional therapeutics" can hardly justify the placing of typhoid fever in the section dealing with diseases of the digestive tract.

For the consideration of a particular disease the discussion of the treatment of typhoid fever was chosen. There are some points which deserve notice, thus the author says that "it should be remembered that the stools must be green and inoffensive. . . ." Now green stools do occur in typhoid fever, but this is rare and it is hard to understand why they must occur. The direction that "there must be no gas pains" seems rather a curious one. The author does not advocate the bath treatment, but this is not surprising when we read his description of a tub bath (p. 28) in which he says "In giving the bath, one should be careful to keep the patient in the water only a minute or two. . . ." It would be interesting to know the authority for this statement; the reviewer knows of none. It is the custom of many writers to pass criticism on the bath treatment of typhoid fever when it is evident that they do not know the method of carrying it out.

There are some descriptions of treatment which do not seem very rational. Thus in endocarditis with valvular insufficiency it is advised "to strengthen the valves by very carefully graduated exercises and passive movements (Schott or Nauheim treatment)." That the object of this or any other treatment is to strengthen the heart valves is a new point in therapy. Under pneumonia it is advised to give atropine to dilate the capillaries and equalize the blood pressure when the skin becomes clammy and pale. This last phrase is not quite clear but as regards any need of *dilating* the capillaries, the usual opinion is that when the circulation is affected in pneumonia, there is too much vasodilation. Then there is a generally accepted opinion that atropine tends to contract the peripheral vessels. Angina pectoris is discussed under the heading of cardiac neuroses and the treatment here given would not carry one far. There does not seem to be any mention of aneurism at all. Broncho-pneumonia is discussed under the heading bronchitis. This perhaps is regional therapy, but it does not seem likely to aid in obtaining a broad view of therapeutics. In gastric hyperacidity a dose of soda of one to two grains is advised, but it is difficult to share the author's view that this will be efficient. In peritonitis "distressing vomiting and peristaltic frenzy are kept in abeyance by careful gastric lavage. The term "peristaltic frenzy" sounds well, but are the bowels not apt to show absence of peristalsis in peritonitis when the stage of vomiting is reached. In several places the author condemns certain methods of treatment, but still devotes space to describing them (for example, the use of gelatine injections on page 275).

It may be argued that a complete discussion of treatment should not be expected in a work with this title but if so there seems little reason for its appearance. The extracts quoted are enough to suggest doubt as to the value of the work and we cannot recommend it. The whole idea of the book seems a step backward.

Nephrocoloptosis. By H. W. LONGYEAR, M. D., etc. (*St. Louis: C. V. Mosby Company, 1910.*)

As the title suggests this interesting little volume is an exposition of a relationship supposed to exist between nephroptosis and coloptosis. The interest centers about the nephrocolic ligament, a structure which the author claims to have discovered. It is described as consisting of a number of fasciculi of fibrous tissue, which can be anatomically grouped and easily demonstrated as thus forming a definite band or ligament of considerable tensile strength extending between the right kidney and the ascending colon, and between the descending colon and the left kidney. The fibrous network of this ligament is continuous with that of the fatty capsule of the kidney.

Nephroptosis without coloptosis, it is boldly asserted, does not occur. In fact the prolapsed colon, weighted down with accumulated fecal masses as a result of associated constipation, and tugging on the right kidney by means of the nephrocolic ligament is considered the principal contributory etiological factor in movable kidney.

Acting upon this idea the author has devised an operation for the correction of nephroptosis the essential feature of which is the utilization of the nephrocolic ligament as a substantial supporting structure.

There are chapters dealing with the subject of movable kidney from the standpoints of Anatomy and Pathology, Etiology, Symptomatology, Diagnosis and Treatment; and at the end is appended a somewhat detailed report of 54 cases of nephrocolopexy in substantiation of the author's claims.

The illustrations are numerous, clear and helpful; and the publishers' work is creditably done.

The book will doubtless stimulate surgeons generally to search very carefully for the nephrocolic ligament in all cases operated upon for nephroptosis. It seems very strange that such a definite anatomical structure, of such vital importance etiologically in a

relatively common disorder, as described and pictured by Dr. Longyear should have escaped notice so long. But judgment as to its real worth must be withheld, of course, until the author's claims have been thoroughly tested by other surgeons. Any definite contribution to the study of movable kidney from an etiological standpoint should be gratefully received, and justly merits careful consideration, in view of the present chaotic state of our knowledge upon this subject. For one cannot help being impressed by the curious discrepancies and radical differences of opinion met with when comparison is made between the views of different authors who have made a special study of movable kidney. Thus, for example, F. W. Griffith (Johns Hopkins Hosp. Bull., XXI, 75) who made a very elaborate and painstaking study of body-shape in relation to movable kidney, concluded that faulty body-shape is more important as an etiological factor than all others combined.

Not so Longyear, however, who holds this to be only one of many minor contributory causes, regarding chronic constipation in its relation to coloptosis as of very much more importance. Thus he explains the much greater frequency of right-sided nephroptosis, since fecal matter does not accumulate in the descending colon; and his statistics show that of 155 cases of movable kidney found among 1000 women examined, he met with not a single case occurring on the left side alone.

Griffith, on the other hand, reports from a study of both clinical and operative statistics at the Johns Hopkins Hospital that the correct proportion of right- to left-sided nephroptosis is about three to one! He found furthermore that a history of constipation was obtained in 49 per cent of white women and 70 per cent of colored women; or, as he says, "White women in whom movable kidney is common do not suffer from constipation as frequently as do colored women in whom movable kidney is uncommon."

It is evident, therefore, how far we are from any uniformity of opinion upon this subject at present, and Dr. Longyear is to be congratulated on having contributed in this attractive little volume so much food for reflection, which it is safe to predict will stimulate the surgical world to speedily interest itself in a thorough test of his original suggestion. E. H. RICHARDSON.

Andreas Vesalius, The Reformer of Anatomy. By JAMES MOORES BALL, M. D., St. Louis. Quarto size (10 x 12¾ inches), printed on heavy Normandy vellum, deckle edge, with heavy extension cover to match. A de luxe volume, issued in the highest style of the typographic art as regards page format, type cutting, decoration and solidity of ink. Pages XVII + 149. Fully illustrated. Price $5.00. (*St. Louis: Medical Science Press, MDCCCCX.*)

There has long been need of a publication in English giving, in readable form, the available data in regard to Vesalius. Burggraeve's Mémoire (Gand, 1841) and Roth's scholarly biography (Berlin, 1892) have largely supplied this want for a French and German reading profession. It has been a regret to all, interested in Medical History, that the promised "Vesalius" in the Masters of Medicine series has never appeared, for what is wanted is such a life of Vesal as Paget gave us of John Hunter and Power of William Harvey in this series. Doubtless Dr. Taylor found it a large task, and in view of Professor Roth's exhaustive study covering many years of labor, there must have been hesitation to enter the same field. However, there may always be something new for the subsequent biographer—*vide* the long series of Harvian orations—and Roth himself has shown, by a number of later papers, that the last word on Vesalius was by no means said in his comprehensive volume.

There are many points of view from which a biographical sketch may be written, and Roth's much annotated "Andreas Vesalius" would, if translated, probably make rather dry and uninteresting reading for the average physician. Few combine the scholar's knowledge with a style suited to all readers.

Though Dr. Ball makes no pretense of having made original studies, his narrative will give to English readers, unfamiliar with Roth and Choulant, a pleasant and helpful picture of Vesal, his contemporaries and his times.

For its interesting introductory chapters and for the review of anatomy in ancient times, it is to be hoped that the volume will be largely read, but as a picture of Vesalius it falls short of one's expectations. The narrative is broken up by the insertion of fragmentary and isolated biographies of Vesal's forerunners and contemporaries to the distraction of the reader's attention from the main theme. To really do justice to the subject would require the pen of a Henry Morley and a knowledge of the 16th century equal to his, and one could wish that he had added a Vesalius to his Jerome Cardan and his Palissy the Potter. His short sketch in Fraser's Magazine in 1853 is an indication of what might have been expected, and he did us a service—to which Dr. Ball refers—in calling Vesal the Luther of Anatomy.

Not only in its content, but typographically, the volume has much deserving of commendation. The Medical Science Press is to be congratulated on the appearance of the work, and the proofreader, on the scarcity of typographical errors. An "of" is missing from line thirteen, page 76, etc. The book is printed on heavy paper, Normandy vellum, imported from France—a commentary on the protective tariff—which takes the type and blocks of the numerous illustrations as no American made paper can. Unfortunately it has been necessary to use two qualities (pages 81-96 in the copy used for review). The index would seem to be unnecessarily elaborate—a rare and perhaps a good fault.

The attention of medical students should be directed to this volume, though it is rather too expensive a work for the majority of them to hope to possess. H. C.

Urinary Surgery—A Review. By F. S. KIDD, M. B., B. C. (Cantab.), F. R. C. S. (*London: Longmans, Green & Co., 1910.*)

In the preface the author states that his purpose is to supply practitioners of medicine with a practical treatise which will aid them in becoming more familiar with the diseases of the urinary system.

The book, of 412 pages, is divided into five sections: 1. Diseases of the Kidney; 2. Diseases of the Ureters; 3. Diseases of the Bladder; 4. Diseases of the Prostate; and 5. Diseases of the Urethra.

English medical books are usually carefully written; this one, however, is a striking exception, for the English shows a violation of most of the rules of rhetoric and a careless use of those of grammar. Ideas of slight relation to one another are connected by conjunctions and jumbled together in the same sentence; prepositions are misued, verbs are omitted, inelegant expressions are injected here and there, and words are often used which inaccurately express the meaning intended. There is almost an entire lack of coordination and unity in the long sentences and many of them require a second or third reading before the author's meaning is apparent.

A few examples of the author's English construction may be quoted: "The patient should lie up in bed, with the foot-end slightly raised, either on her back, or on her right side, and the attack will pass off in a few hours." "Stone is the commonest cause of single cyst in the kidney met with at operation." Referring presumably to the X-rays which were spoken of in a preceding sentence, he says, "Before their advent stones were approached in the dark." "Intervals of years may intervene." "The symptoms cool down." "The abscess breaks on to the skin." "A triangular shadow in the renal region with a nose

pointing downwards with phosphatic urine means ureteric block, ..." and "gross parasites such as hydatid cysts."

The arrangement of the subject matter in short paragraphs with distinctive headings is faulty and in many instances very confusing.

It does not seem necessary in a work of this kind to give the embryology of the kidney and ureter; if the reader does not know it beforehand, he will not be much enlightened after having read the synopsis.

In what should be a very important chapter on renal calculus, there is nothing new, and the arrangement of the facts given is so poor that a clear idea of the subject cannot be obtained.

The discussion of new growths of the kidney is very inadequate, in many places being reduced to simply a naming of the conditions. Inflammations of the bladder and prostate are somewhat better handled, but here again the author falls short.

The pathological descriptions in various chapters for the most part show crudity and unfamiliarity with this part of the subject. Expressions such as "The pathology of spread," "the giant cell systems," "degeneration of the higher cells of the kidney" seem to be without warrant.

In a book intended for practitioners symptomatology is the most important feature, but the signs and symptoms are divided into so many sub-headings and so scattered in various paragraphs and in general so inadequately dealt with that a comprehensive grasp of them is rendered impossible.

In the section on tuberculosis of the kidney in speaking of catheterization of the ureter, the following astounding assertion is made: "Before removal, half an ounce of a one per cent solution of corrosive sublimate is injected through the catheter." This surely would kill all the tubercle bacilli which might have been artificially introduced, but at the same time, it would destroy the ureter and pelvis of the kidney. Another statement in the chapter on Tuberculosis of the Bladder, while not dangerous, is certainly erroneous: "If a young man without venereal taint who usually sleeps well is constantly awakened at night by desire to micturate, the diagnosis is tuberculosis of the bladder."

The treatment of certain diseased conditions is short and in many instances too cursory to be of much help. The operative technique is so briefly described that it is questionable whether any mention of it need have been made.

There is much good material in the book; the author's advice for the most part is sound, his insistence on a thorough examination at the onset of various maladies is commendable, and the surgical principles which he sets forth are, with a few exceptions, correct. If the whole text were entirely rewritten in passable English, the subject matter rearranged, the errors corrected and numerous repetitions omitted the book would have some value; but as it stands, it is at best of doubtful utility.

The Sexual Disabilities of Man, and Their Treatment. By Arthur Cooper, Consulting Surgeon to the Westminster General Dispensary, etc. Second edition. Revised and enlarged. Price $2. (*New York: Paul B. Hoeber, 1910.*)

The book is divided into two sections: (1) Sterility and (2) Impotence.

In the first, the author discusses the normal and abnormal characteristics of the seminal fluid, the changes found in the spermatozoa, the various physical defects, and the most common diseases which are held responsible for sterility. At the end treatment is advised for the most usual and important changes found.

Impotence is dealt with under two headings: Secondary and Primary. (1) Secondary impotence is caused by definite morbid conditions such as physical defects and local and general disease. (2) Primary impotence is mainly nervous in origin and only slight, if any, local changes are demonstrable. Three main factors are discussed: (1) The psychical element; (2) The effect of abnormal seminal emissions; and (3) The result of irritation or over-stimulation. At the end a fairly comprehensive treatment is given.

The book is well and pleasantly written and covers the ground in a fairly satisfactory manner, but in a few places the author has been too brief, and in others, matter has been inserted which might well have been left out. The practitioner or student who knows very little of the subject may find the work helpful, but for those who are conversant with the literature it will have almost no value.

Surgical After-Treatment. By L. R. G. Crandon, A. M., M. D., Assistant in Surgery at Harvard Medical School. Illustrations. Price $6. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

There are very few surgeons who have not at one time or another, in the course of their career, felt the need of a good book on "Surgical After-Treatment." Especially helpful must such a work be to the surgical beginners.

This long felt want is now beautifully supplied by Dr. Crandon, who is to be congratulated on the success of his book.

Starting out with a chapter on the Sick Room, Nurses' Chart, Posture, other chapters follow telling in clear, concise language of the care of the patient before and after operation, the anæsthesia, feeding, care of the wound, complications, etc.

Further on in the book the various operations are taken up one by one and dealt with specifically, such as for instance the Radical Cure of Hernia, Strangulated Hernia, Curettage for Abortion and Miscarriage, etc.

The last two hundred pages of the book are devoted to "Therapeutic Immunization and Vaccine Therapy," written by Dr. George P. Sanborn, also of Boston. This is a wise addition to the work as every modern surgeon must be familiar with this growing branch of medicine.

But, perhaps the most commendable feature of the whole book is the fact that it is distinctly not a narrow and detailed account of the methods and procedures of one hospital or one institution, but rather a sort of condensation, a résumé of the best methods in use at the present day in the various hospitals, both of this country and of Europe. One has only to glance at the numerous and well-chosen references to the literature to appreciate the truth of this statement. Bertram M. Bernheim.

Practical Pathology. By J. Sims Woodhead, M. A., M. D., LL. D., Fellow of the Royal Society of Edinburgh; Professor of Pathology in the University of Cambridge. Illustrated. Fourth Edition. Price $11. (*London: Oxford University Press, 1910.*)

The welcome accorded the previous editions of Prof. Woodhead's book is possibly the best indication of the need of a text of this type. As so much time has elapsed since the appearance of the third edition, it will be well to briefly review the scope of the volume.

The first chapter deals with a method of performing post mortem examinations, the requisites necessary, etc. The only criticism one can offer is whether it is really of advantage to devote much space to a subject which can only be learned by observation or by actual experience.

The second chapter deals with pathological technique. By the time he reaches his course in pathology the student should be familiar with the microscope. On the other hand his knowledge of the examination of fresh tissue is limited and this portion of the chapter is more satisfactory. The advantages of the study of fresh tissues and injected organs have been neglected to a great extent with the extensive use of microtomes and improved stain-

ing methods, and it is therefore the more important to emphasize the study of fresh tissue as the author does. This is followed by a rather complete description of hardening, embedding and staining methods which is doubly valuable since each method is numbered and these numbers are used continuously through the text as guides for the best methods available in the study of specific lesions. This reference system simplifies the student's work greatly inasmuch as it puts a definite mode of procedure at his disposal for most cases; it is possible, however, that just this precision may be a disadvantage since it will not necessitate any discriminating thought on the part of the student.

The third chapter on inflammation begins in the only logical manner, *i. e.*, the description of cells found in the blood and in inflammation. The description is objective with only sufficient theory to impress the unsolved cell genesis problems. The remainder of this chapter deals with inflammation and repair as it occurs in various characteristic tissues. The author's method in this as well as in the description of morbid processes in the subsequent chapters is to be strongly commended. First the gross lesion is described, then after the most appropriate manner of hardening and staining the tissue is given, the microscopic examination under definite low and high magnification is detailed. Many of these latter descriptions are more valuable on account of the excellent illustrations. In some instances these are diagrammatic and possibly more valuable for this reason.

The book is unique, its scope is different from every other treatise on pathology and is no doubt just the thing most needed by the student since it puts at his disposal ready methods for the study and interpretation of the usual lesions of pathological anatomy.

The price of this book, however, precludes any very extensive use.

Scientific Memoirs—New Series No. 37. By Officers of the Medical and Sanitary Departments of the Government of India.

Investigations on Bengal Jail Dietaries with Some Observations on the Influence of Dietary on the Physical Development and Well-Being of the People of Bengal. By CAPTAIN D. MCCAY, M. B., etc. Issued under the authority of the Government of India by the Sanitary Commissioner with the Government of India, Simla. Price 4/3. (*Calcutta: Superintendent Government Printing, India, 1910.*)

A very long and thorough report divided into 2 parts, preceded by an Introduction. Part I is divided into 5 chapters: 1, The Food-Stuffs of Bengal Jail Dietaries; 2, The Nutritive Value of Bengal Jail Dietaries; 3, Report on Six Months' Use of Special Diets in Puri Jail; 4, The Effects of the Large Quantity of Salt Given in Bengal Jail Dietaries; and 5, Some Side-Issues of the Investigation. Part II discusses "The Relationship of Food to Physical Development." The special nature of this report makes it one of interest only to the physiologist, or a few students especially devoted to problems of metabolism; such men will find it well worth a careful study.

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CIRRHOSIS OF THE LIVER. FIVE DIFFERENT TYPES OF LESIONS FROM WHICH IT MAY ARISE.[1]

By F. B. Mallory, M. D.

(From the Pathological Laboratory of the Boston City Hospital.)

Introduction.—In some organs the late stages of certain lesions have received more attention than the beginnings of these lesions. The emphasis has been placed on the wrong end of the process. This statement is particularly true of the inflammatory changes in the liver and in the central nervous system.

Now, in order to understand a pathological process, it is necessary to find and study its beginning and to trace its biological development. It is with this view in mind that I shall present to you to-night a study of five different types of early lesions of the liver so that you may see for yourselves how the late stages of these lesions resulting in sclerosis would all be classed under the term cirrhosis. It will enable you better to appreciate what very different kinds of pathological processes the term covers.

I shall not present these different types of lesions in the order of their relative frequency and importance, but in such sequence as will throw most light on certain features common to them all, especially the changes in the connective tissue stroma.

To the clinician the term cirrhosis usually means a chronic, progressive, destructive lesion of the liver combined with reparative activity and contraction on the part of the connective tissue. This contraction of the connective tissue may lead to obstruction of bile ducts, causing more or less jaundice, and to interference with the flow of blood through the blood vessels resulting in portal congestion and ascites.

The pathologist uses the term cirrhosis in a broader sense. He applies it to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue. It is from the pathologists' point of view that I approach the subject.

I shall have to refer first to three pathological conditions which may complicate some of the changes terminating in sclerosis.

The first of these, fatty infiltration, is common but of little significance except that under certain conditions the fat present in the cells seems to serve as nutrition and thus aids to protect to some extent the liver cells containing it from undergoing necrosis as readily as surrounding cells containing none.

The second is chronic passive congestion. When this condition is uncomplicated it seems not to cause disappearance of the liver cells around the hepatic vein in the lobule as is generally taught. The cells disappear as the result of a toxic necrosis complicated with hemorrhage. If, as is usually the

[1] Read before the Johns Hopkins Hospital Medical Society, Nov. 7, 1910.

case, the necrosis is recent, due to a terminal infection, it is easy to demonstrate the necrotic liver cells in the midst of the red blood corpuscles filling the trabecular spaces. If the necrosis is of longer standing the necrotic cells will have partially or entirely disappeared under the solvent action of polynuclear and endothelial[2] leucocytes. The trabecular spaces, dilated and filled with blood, are readily mistaken for distended sinusoids. As a matter of fact the sinusoids are usually more or less compressed as the result of the hemorrhage. In time the hemorrhage disappears and the sinusoids again dilate. Owing to the condition of congestion the liver cells do not regenerate. Consequently, in time, the trabecular spaces shrink and the connective tissue contracts and thickens, although it does not increase in amount, and the liver by its consistence may suggest a mild uniform type of sclerosis.

The third and most important pathological condition to which I must refer is general bile stasis due usually to obstruction of the common bile duct by a calculus or by a tumor. This condition leads to marked dilatation of the bile capillaries around the hepatic vein, to rupture of them, and to the escape of masses of inspissated bile into the lymph space between the liver cells and the wall of the sinusoid. Here the bile is incorporated by endothelial leucocytes and gradually dissolved. After solution it seems to pass, perhaps by osmosis, directly into the blood stream, not along the lymph channels to the thoracic duct. Apparently uncomplicated bile stasis does not result in any sclerotic process around the hepatic veins where the chief lesion is located and it certainly does not around the portal vessels.

I. Toxic Cirrhosis.

A fairly common affection of the liver is necrosis of the cells around the hepatic vein, the so-called central necrosis, due to toxins in the circulation. It is a frequent terminal lesion. Occasionally the necrosis is limited more or less definitely to the midzonal region. This type of lesion may be slight, or very extensive involving nearly all the cells in a lobule. It is usually quite uniformly distributed throughout the whole liver. In the milder degrees of necrosis the liver cells are quickly invaded by polymorphonuclear or endothelial leucocytes (Fig. 1) or by both, dissolved, and removed. If the patient survives, the liver cells usually regenerate and the liver lobules are restored to their normal appearance. Sometimes, however, the liver cells do not regenerate. Then the walls of the sinusoids collapse, the lobules shrink, and the connective tissue around the hepatic veins appears thickened, just as may happen in connection with chronic passive congestion. Experimentally it has been shown that this form of lesion may be produced by chloroform narcosis and that regeneration will quickly take place.

Occasionally this type of necrosis is very extensive so that in some lobules every liver cell is killed. If the patient survives, the necrotic liver cells are invaded and so quickly removed by the action of leucocytes (Figs. 2 and 3) that in five or six days the liver will diminish in weight from 1500 grams to 600 or 500 grams or even less. The liver will be perfectly uniformly lessened in size, and flabby to the touch. This is the early stage of so-called acute yellow and red atrophy of the liver. If the patient still survives, active regeneration takes place, the liver cells giving rise to new liver cells, bile duct epithelium producing bile duct epithelium. As a result of this active regeneration those parts of the liver where liver cells persist rapidly enlarge and the lobules assume more or less completely their former shape, or perhaps undergo compensatory hypertrophy. These are the yellow bile-stained areas of acute yellow atrophy of several weeks' duration. In those parts of the liver where all the liver cells were killed, the bile ducts (Figs. 4 and 5) grow a third or half the way towards the hepatic vein and then stop. They do not produce liver cells. The lobules are much diminished in size, the leucocytes disappear from the trabecular spaces, the sinusoids are dilated. These are the red parts of a case of acute yellow atrophy of two to several weeks' standing.

This type of lesion teaches two things that are of importance in considering the other types of lesions which result in cirrhosis. First, that simple necrosis of liver cells without injury to blood vessels and connective tissue stroma, does not result in proliferation of connective tissue. The connective tissue which is there shrinks together and thickens, leading to an apparent but not real increase of it. Second, that liver cells regenerate only from liver cells. The bile ducts lengthen owing to proliferation of bile epithelium but they cannot form liver cells.

Various degrees of this series of lesions known under three different names, central necrosis, acute yellow and red atrophy, and cirrhosis, are not, I believe, so infrequent as is generally supposed. It ought to be possible to recognize the resulting type of cirrhosis long after the acute lesion is over even without a clinical history to help. Two points are of diagnostic value: the very irregular distribution of the connective tissue as seen on gross examination: and the preservation of the shape of the lobules, much shrunken, in the sclerosed parts. Whether or not continued contraction of the connective tissue may in time lead to obstruction of bile ducts and blood vessels resulting in jaundice and ascites, I am at present unable to say.

It is of interest that this type of cirrhosis is of acute origin; therein it differs from the four other varieties which are all of a more or less chronic nature.

[2] The endothelial leucocyte arises by proliferation and desquamation of endothelial cells lining blood and lymph vessels. It emigrates from vessels like the other leucocytes, multiplies by mitosis in the vessels and tissues like the lymphocyte, and possesses one especially distinguishing property, that of being under certain circumstances very phagocytic for the other leucocytes as well as being able to incorporate red blood corpuscles, various microorganisms, and foreign bodies of all sorts. This leucocyte is known by various names, the large mononuclear of the blood, the nongranular leucocyte, the macrophage, etc. Its origin is best studied in the early lesions of typhoid fever, in very young miliary tubercles, and experimentally by the subcutaneous injection of agar.

II. Infectious Cirrhosis.

The second type of cirrhosis I shall term infectious cirrhosis because it is due to the presence of bacteria in the lesions. In my experience it is comparatively rare. Bacteria may and do gain access to the liver by direct continuity and through the hepatic artery, the portal vein, and the bile ducts. It is only of infection through the bile ducts that I shall speak here, as this seems to be the only form of bacterial infection which leads to a dictinct form of cirrhosis.

Infection through the bile ducts, when there is bile stasis from gall stone or other obstruction, not infrequently leads to infection with various bacteria and to necrosis (Fig. 9), abscess-formation, and death. A rarer form of invasion sometimes takes place along apparently normal bile ducts and leads to a very characteristic type of cirrhosis. It is to this variety of infection that I wish to call your attention.

My experience of the early stages of the process is limited to two livers which agree very closely in their gross and microscopic appearances although the infection is of longer duration in one than in the other. Both were from children, a girl [3] of twelve and a boy [4] of three. At post mortem examination the livers were two to three times the normal size and much increased in consistence. The surface and cut section were smooth. Clinically jaundice and enlargement of the liver were prominent symptoms.

What the infecting organism is I do not know as infection was not suspected and no cultures were taken. The bacteria present in the acutest lesions in the girl are slender bacilli (Fig. 7). In many ways the lesions in the liver may be said to correspond to the chronic process produced in the kidney by the colon bacillus.

Infection is spread chiefly through the bile ducts but the organisms have also invaded the surrounding connective tissue and are spreading through it. The pathological changes are confined almost entirely to the region around the portal vessels and are extending quite uniformly toward the hepatic vein of each lobule. The lesion is by nature chronic. It is active and spreading in many places; quiescent and healing in others.

The bile ducts (Fig. 8) frequently show more or less dilatation and in some places are filled with polymorphonuclear leucocytes (Fig. 10), in other places with endothelial leucocytes (Fig. 8). Here and there where the process is active the bile duct epithelium is necrotic or gone and the exudation is spreading into the surrounding tissue (Fig. 10). Here the bacteria lead to necrosis of the liver cells, of the blood vessel endothelium and of the fibroblasts, and to an acute inflammatory exudate consisting of polymorphonuclear leucocytes and fibrin. Where the process is less active and the bacteria have died out the exudation consists chiefly of endothelial leucocytes many of which are phagocytic and contain fragments of cells. Mitotic figures in endothelial leucocytes are found occasionally. Lymphocytes are present in relatively small numbers. The lymphatics (Fig. 6) in the capsule of the liver are in places distended and filled with endothelial leucocytes and a little fibrin.

Proliferative activity on the part of the fibroblasts is well marked and evidently follows the direct injury done the connective tissue cells by the toxins from the bacteria; in other words it is simple regeneration.

As a result of the exudation around the portal vessels, of the encroachment of the process on the liver cells, and of the proliferative activity on the part of the fibroblasts, the portal tissues show up as broad bands running very regularly between the lobules of the liver cells (Fig. 11).

In those parts of the liver where the lesion is older and the exudation is less active the bile ducts are more or less dilated and often appear considerably increased in number as though a diffuse bile duct adenoma were present. This appearance is probably due to contraction following marked dilatation and stretching of the ducts when the lesion was more acute. In those parts of the liver where complete repair has taken place this same apparent increase in the size and number of the bile ducts in the midst of abundant scar tissue is still noticeable, at least in the early cases.

In many places the inflammatory exudation in the smaller bile ducts has led to occlusion of them and to obstruction to the outflow of bile which appears in the ducts and bile capillaries above the point of obstruction in the form of yellowish green inspissated masses. The obstruction is focal only, not general and complete; therefore, the resulting jaundice is not intense.

The characteristics of this type of cirrhosis, while the infectious process is still active, are apparently the following:

The lesion spreads very uniformly from the portal vessels toward the hepatic veins, rarely cutting into a lobule. As a result the true lobular arrangement is more or less perfectly preserved. The bile ducts are often dilated and tortuous, so that they appear increased in number. The injury done the fibroblasts leads to active regeneration on their part and to the production of abundant connective tissue. As the result of the extensive inflammatory exudation and of the regeneration of the connective tissue the liver is much increased in size. The surface and cut section are comparatively smooth, perhaps owing to the even distribution of the inflammatory process.

Two cases of congenital jaundice with a uniformly distributed cirrhotic process and obliteration of the common bile duct show microscopically a marked increase of connective tissue around the portal vessels and are undoubtedly due to intrauterine infection extending along the bile ducts (Fig. 12).

III. Pigment Cirrhosis.

A third form of cirrhosis which deserves mention is that known as pigment cirrhosis, occurring in cases of hemochromatosis. It appears to be due entirely to mechanical causes. Endothelial leucocytes filled with blood pigment collect often in great numbers in the lymphatic spaces and vessels

[3] Autopsy by Dr. O. R. Mabee.
[4] Autopsy by Dr. H. A. Christian.

of the liver, chiefly around the portal vessels (Figs. 13 and 14) but to some extent around the hepatic vein and irregularly throughout the lobule between the liver cells and the walls of the sinusoids. Whether they emigrate from the sinusoids after becoming filled with pigment, or absorb it like the liver cells and bile epithelium from the hemoglobin dissolved in the serum and lymph cannot be determined. But after they are filled with pigment they unquestionably are able to migrate. Wherever they collect in numbers they seem to injure the connective tissue mechanically by stretching it. In consequence there is a certain amount of regeneration on the part of the fibroblasts so that more or less sclerosis (Fig. 14) is produced.[5]

A similar increase of connective tissue is caused in the same way under similar conditions in the pancreas, adrenals, and lymph nodes. In time more or less of the pigment is dissolved by the action of the endothelial leucocytes, which then disappear, leaving the connective tissue behind as the only remains of the process.

This lesion, like infectious cirrhosis, may result in the acute stage in a large, smooth liver weighing in one instance, from a woman, 2500 grams. The primary injury seems to be done to the connective tissue. By contraction of this connective tissue later, more or less injury is probably caused to the liver cells.

The sclerosis which occurs in the liver and other organs in the pathological condition known as hemochromatosis is perfectly analogous to that which takes place in the lungs and peribronchial lymph nodes as the result of the inhalation of large amounts of carbon. Endothelial leucocytes carry much of the pigment into the walls of the alveoli and from there to the lymph spaces and vessels around the bronchi and larger blood vessels. Many of the cells remain packed in these situations and lead to considerable increase of the connective tissue.

Many of the cells in the lymphatics are carried to the peribronchial lymph nodes. At first they lie free in the lymph sinuses but soon migrate into the parenchyma when they lead to increase of connective tissue and secondarily to gradual disappearance of the lymphocytes. Some of the endothelial leucocytes filled with pigment migrate into the capsule of the lymph node and into the adjoining fat tissue.

This type of cirrhosis is characterized by pigmentation, by a very uniformly distributed increase of connective tissue, and by a smooth surface of the liver, externally and on section. It may attain a fairly large size. The increase of the connective tissue seems to be due to mechanical causes only.

IV. Syphilitic Cirrhosis.

Syphilitic infection of the liver is usually divided into two types, the congenital and the acquired. In the congenital type a diffuse lesion predominates, in the acquired a focal lesion; but the two types of lesions are often combined in the congenital form and may coexist to some extent in the acquired.

[5] See Cirrhosis Hepatis Anthracotica, by W. H. Welch, Johns Hopkins Bulletin, 1891, vol. II, 32, where I should interpret the origin of the sclerosis in the same way.

The primary, essential lesion produced by the treponema pallidum is best studied in chancres removed before necrosis has begun and in the liver and other organs of cases of congenital syphilis. The so-called tertiary lesions would probably be equally serviceable for study if they could more often be obtained before the stage of necrosis.

In studying syphilitic lesions it is necessary at our present stage of technical development, to prepare two parallel series of sections, the one stained by Levaditi's method after fixation in formaldehyde so as to demonstrate the causative agent, the other by various methods after fixation in Zenker's fluid to show the tissue reaction. When this is done it is found that the treponemata, present often in great numbers in the primary as well as in the congenital lesions, are situated in the minute lymph spaces between the cells and especially between the fibrils. They occur most numerously in the connective tissue between the collagen fibrils everywhere within the area invaded including that in the intima of arteries and veins. The injurious action of the organisms is exerted chiefly if not exclusively on the fibroblasts which are thereby stimulated to active regeneration, as a result of which much fibrous tissue is produced. This leads in part at least to the hardness of the primary lesion and to the sclerosis of the liver and other organs in congenital cases.

In the congenital lesions the tissue reaction often does not go beyond this stage. In the primary and tertiary lesions, however, the reaction is more intense. As a result there is added to this proliferation of fibroblasts an inflammatory infiltration consisting chiefly of lymphocytes including plasma cells, often also of numerous eosinophiles. Under certain conditions giant cells are formed from the endothelium lining the smaller blood vessels and also perhaps the lymph vessels. These giant cells may occur in chancres, in gummata, and especially in tertiary lesions of the skin. They are due to the presence of the treponemata within the blood and lymph vessels and to their action on the endothelial cells. The resulting giant cells often contain treponemata in large numbers.

The same lesion of proliferation of fibroblasts taking place in the walls of veins and arteries, especially in the intima, leads to narrowing and more or less complete occlusion of many of the smaller vessels. The areas thus deprived of nutrition gradually undergo necrosis (gumma formation) which results in an active inflammatory exudate of serum and of endothelial leucocytes (cascation); less often of polymorphonuclear leucocytes (suppuration). With the occurrence of the necrosis and of the acute inflammatory exudate the treponemata as a rule rapidly disappear from the lesion and the area affected tends in time to heal, owing to a local immunity being apparently produced by the leucocytosis. In this respect the focal lesions in syphilis differ materially from those in tuberculosis which tend to spread indefinitely.

Reverting now to the liver we find that in congenital syphilis the treponemata injure primarily the connective tissue cells, especially those lying between the liver cells and the walls of the sinusoids. As the result of the active and con-

tinued proliferation of the fibroblasts due to efforts at regeneration, the connective tissue increases greatly in amount. This is shown by the fact that where the treponemata are most numerous (Fig. 15) the connective tissue is most abundant (Fig. 16). Later as the collagen fibrils contract the liver cells are compressed and more or less atrophy accordingly results. This diffuse type of lesion, due to primary increase of connective tissue and secondary atrophy of liver cells, is perfectly well recognized as characteristic of congenital syphilis. It is not infrequently complicated with focal lesions (miliary and larger gummata) due to occlusion of the sinusoids, necrosis of the liver and other cells in the area affected, and inflammatory infiltration with serum and polymorphonuclear or endothelial leucocytes.

In acquired syphilis the early lesion in the liver is diffuse (Fig. 17) and similar to that in congenital syphilis but occurs in larger and smaller foci only and usually leads to necrosis and inflammatory infiltration, forming the characteristic gummata of this type of infection, which later may heal and contract, resulting in deep scars and more or less lobulation of the liver.

If this reading of the lesions occurring in syphilis is correct, then although the gross manifestations are many and varied, the cellular reaction caused by the treponema pallidum is essentially the same in all of them and varies only in degree, due to varying conditions of injury and reaction and of local and general immunity.

V. Alcoholic Cirrhosis.

In the chronic, progressive, so-called alcoholic, type of cirrhosis there occurs a peculiar form of necrosis of the liver cells, which seem to be characteristic of it. The cytoplasm of the cells first undergoes a degenerative change in consequence of which an irregular, coarse, hyaline meshwork (Fig. 18) appears in it. This meshwork stains deeply with eosin and with phosphotungstic acid hematoxylin after fixation in Zenker's fluid. This degenerative change may attack single cells or small or large groups (Fig. 19) of them: it may occur focally or very diffusely. The affected cells may be situated in any part of the lobule, but lie most commonly, perhaps, in the region of the portal vessels, and sometimes are sharply limited to that location.

The affected cells and the nuclei within them are usually swollen. After the hyaline change has reached a certain degree of intensity the cells are surrounded and invaded by numerous polymorphonuclear (Fig. 20) or endothelial (Fig. 22) leucocytes (sometimes the one, sometimes the other), which dissolve the cells, the hyaline material last, and thus bring about their disappearance.

Along with this hyaline change and destruction of the liver cells there occurs active regeneration as evidenced by occasional mitotic figures in adjoining liver cells. There is also more or less proliferative activity on the part of the fibroblasts resulting in increase of connective tissue.

These different processes of hyaline degeneration ending in necrosis, of leucocytic infiltration, of regeneration of liver cells, and of increase in the amount of connective tissue, when extensive, diffuse, and acute, lead to considerable increase in the size and weight of the liver (2400 grams in one instance). The surface of such a liver is smooth and on section the cut surface is uniformly even, the lobulation indistinct, and the consistence much increased so that the liver tissue tears with difficulty. In other cases the various changes are much less extensive and hence more chronic because they do not cause death so quickly.

Even in the latest stages of alcoholic cirrhosis, however, it is usually possible to find liver cells undergoing the peculiar hyaline change which seems to be characteristic of this process. Still it is not possible to deny that this destructive hyaline change may cease entirely and leave nothing but the sclerosis as evidence of what has taken place.

The increase in the amount of connective tissue causes trouble later when it contracts by occluding bile ducts and blood vessels here and there throughout the liver. Obstruction of the bile ducts results in focal bile stasis so that scattered areas appear dark green. In these areas the bile capillaries are often greatly distended and in places ruptured so that masses of inspissated bile have escaped into the lymph spaces between the liver trabeculæ and the walls of the sinusoids. Here the masses are taken up by endothelial leucocytes and dissolved just as in the ordinary generalized bile stasis due to obstruction of the common duct.

It is not at all uncommon to find all these different processes (hyaline degeneration, leucocytic infiltration, regeneration, proliferation of connective tissue, and focal bile stasis) present in one and the same liver section.

The obstruction to the general flow of blood through the vessels resulting in portal stasis and ascites needs no mention here.

This type of cirrhosis is very commonly complicated by fatty infiltration (Fig. 21) which leads to marked increase in the weight of the liver (3315 and 3580 grams in two instances, and greater weights are on record). As a rule the clinician's diagnosis of hypertrophic cirrhosis proves to be of this nature. So far as can be determined from histological observation, the presence of the fat interferes in no way with the degenerative process. Cells filled with one or more fat vacuoles undergo hyaline change like the others.

The cause of the increase of the connective tissue in this type of cirrhosis is not perfectly obvious. The primary injury affects the liver cells and is followed by more or less regeneration of them. We have seen perfectly clearly in the first type of cirrhosis (that following extensive central necrosis), that injury to the liver cells does not result in proliferation of fibroblasts. On the other hand we have, in alcoholic cirrhosis, around and invading each necrotic cell, an acute inflammatory exudate of leucocytes which must cause more or less stretching of the connective tissue. The injury which results in proliferation of fibroblasts seems, therefore, as in pigment cirrhosis to be mechanical in origin, not toxic.

If we leave tumors out of the question, the only other common cause, besides direct toxic or mechanical injury to fibroblasts, which stimulates them to proliferate is the presence of fibrin and that plays no part in this form of cirrhosis.

It has long been a much disputed point, chiefly with reference to the alcoholic type of cirrhosis, whether the number of bile ducts in certain cases is greatly increased or whether many of them are not compressed columns of liver cells. The type of necrosis following central necrosis shows that bile ducts may grow out to a considerable distance towards the hepatic vein. In infectious cirrhosis a similar prolongation of bile ducts may occur. On the other hand the diffuse form of syphilitic cirrhosis shows that liver cell trabeculæ may be greatly compressed so as to resemble to some extent bile ducts. Therefore, it is theoretically possible that both true and apparent bile duct formations may occur in alcoholic cirrhosis. As a matter of fact both probably do. If these so-called bile ducts are carefully studied after proper staining it will often be found that in some of the epithelial cells composing them hyaline material similar to that in the degenerating liver cells is present (Figs. 23 and 24). Likewise in alcoholic cirrhosis complicated with fatty infiltration fat vacuoles will occasionally be found in the cells (Fig. 24) which look like bile duct epithelium. The presence of the fat vacuoles and of the hyaline material proves beyond question, it seems to me, that the cells containing them are compressed liver cells and not bile duct epithelium.

The terms hypertrophic and atrophic cirrhosis cause the student and the clinician much trouble. This analysis of these five types of lesions shows that we may get a large, hypertrophied, smooth liver in at least three of them, in infectious, pigment, and alcoholic cirrhosis. It is due in each instance to an extensive, diffuse, acute process. If the acute lesion ceases and healing takes place, or if the process is of moderate intensity and long duration so that healing and scar tissue are more prominent than degeneration and exudation, the liver will diminish in size below the normal. The cirrhotic liver following central necrosis is necessarily at all stages below the normal in weight.

Atrophic cirrhosis simply means a liver in which a large proportion of the liver cells have been destroyed and have disappeared, while the existing and new-formed connective tissue have been rendered unduly prominent.

The terms monolobular and multilobular cirrhosis are also extremely confusing. They state only a relation between masses of liver cells which rarely correspond to liver lobules and strands of connective tissue. They do not in the least explain the nature of the process. In infectious cirrhosis the lesion is confined quite uniformly to the portal vessels: the same is true to a less degree of pigment cirrhosis. If, after old custom, the hepatic vein is taken as the center of the lobule, then these two types of cirrhosis may be said, perhaps, to deserve the term monolobular.

In syphilitic cirrhosis of the diffuse type the sclerosis spreads quite evenly throughout every lobule.

In cirrhosis following central necrosis, large groups of lobules are completely sclerosed, while other large groups may be perfectly normal. The lesion is most irregular in distribution.

In alcoholic cirrhosis the distribution and intensity of the degenerative process vary greatly in different cases, and the increase of the connective tissue follows in the same lines. It often cuts into lobules in every direction. At other times it is fairly regular in its distribution. As a rule, however, the lobular arrangement is quickly distorted. Hepatic veins are hard to find. Sometimes the more normal areas are small, at other times large so that on gross examination either term, mono- or multilobular, might be appropriate. It must also be borne in mind that regeneration of liver cells plays an important rôle in alcoholic cirrhosis and may lead to comparatively large areas of newly formed liver cells, showing no lobular arrangement, containing no bile ducts, and sometimes regarded as adenomata.

It would seem much wiser to discard these terms which do not explain and serve only to confuse. They emphasize the wrong end of a pathological process and represent only the result of two forces acting against each other, the expanding efforts of regenerating liver cells, the contracting force of the proliferated fibroblasts which tend to squeeze the surrounded liver cells into the narrowest compass, namely, into spherical masses.

Granting that cirrhosis may arise in the ways described from at least five different types of lesions, is it possible, in the case of a given sclerosed liver, to determine what the nature of the acute process was to which it owed its origin? I am inclined to think that in most cases, perhaps in all, it is possible to do so, if the characteristics of each type are clearly comprehended and if the sclerosed liver is carefully examined.

Conclusions.

At least five different types of lesions may terminate in cirrhosis (sclerosis) of the liver; one is acute, the other four more or less chronic in character.

Toxic cirrhosis (following extensive central necrosis) demonstrates clearly three facts:

1. That when all the liver cells of a lobule are destroyed the bile ducts grow out a certain distance towards the hepatic vein, but that they do not produce liver cells.

2. That liver cells regenerate only from liver cells, never from bile duct epithelium.

3. That fibroblasts (connective tissue cells) do not proliferate when liver cells alone are destroyed.

The other four types of lesions terminating in cirrhosis show that fibroblasts multiply (regenerate) only when fibroblasts themselves have been injured or destroyed and thus lead to increase of the connective tissue.

The so-called alcoholic type of cirrhosis is characterized by a peculiar hyaline degeneration of the cytoplasm of the liver cells preceding necrosis. In this same type of cirrhosis the contraction of the connective tissue frequently compresses groups of liver cells so that they may resemble bile ducts: in

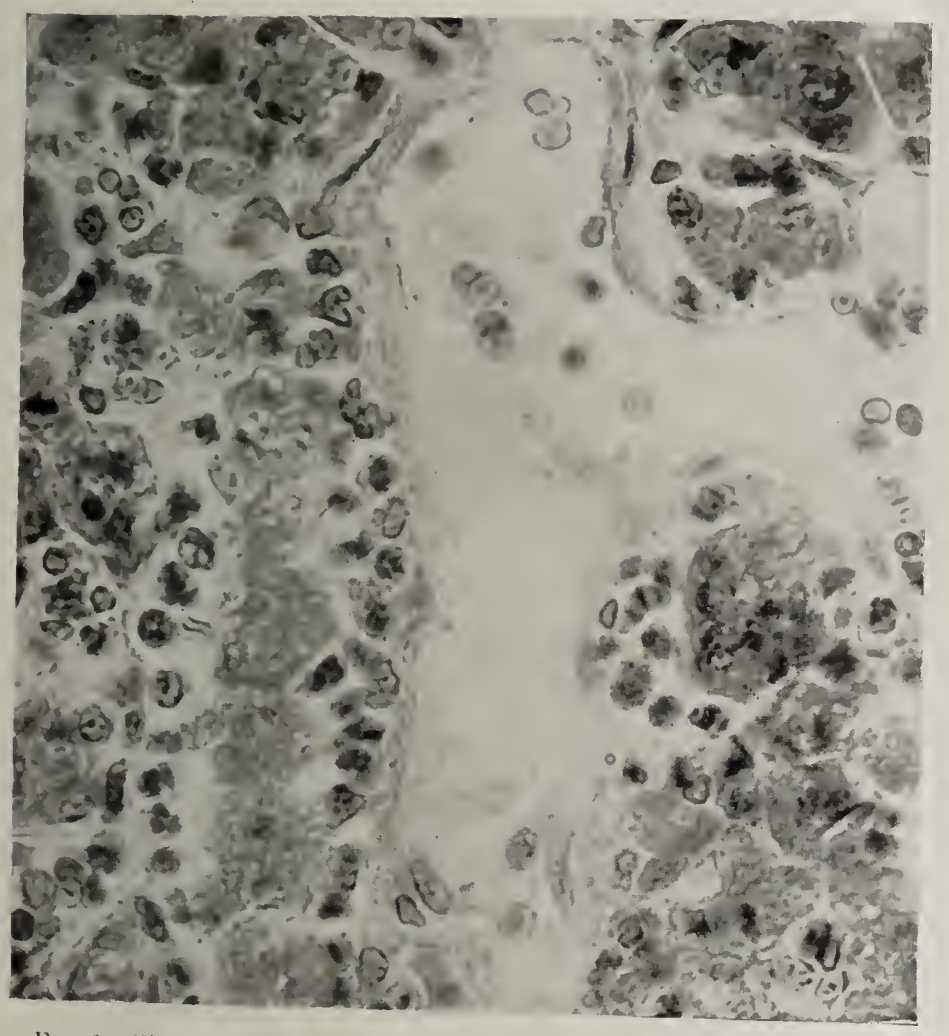

FIG. 1.—First stage of toxic cirrhosis. Necrosis of liver cells around hepatic vein (central necrosis): invasion by polymorphonuclear leucocytes which lie mostly between the necrotic liver cells and the walls of the sinusoids.

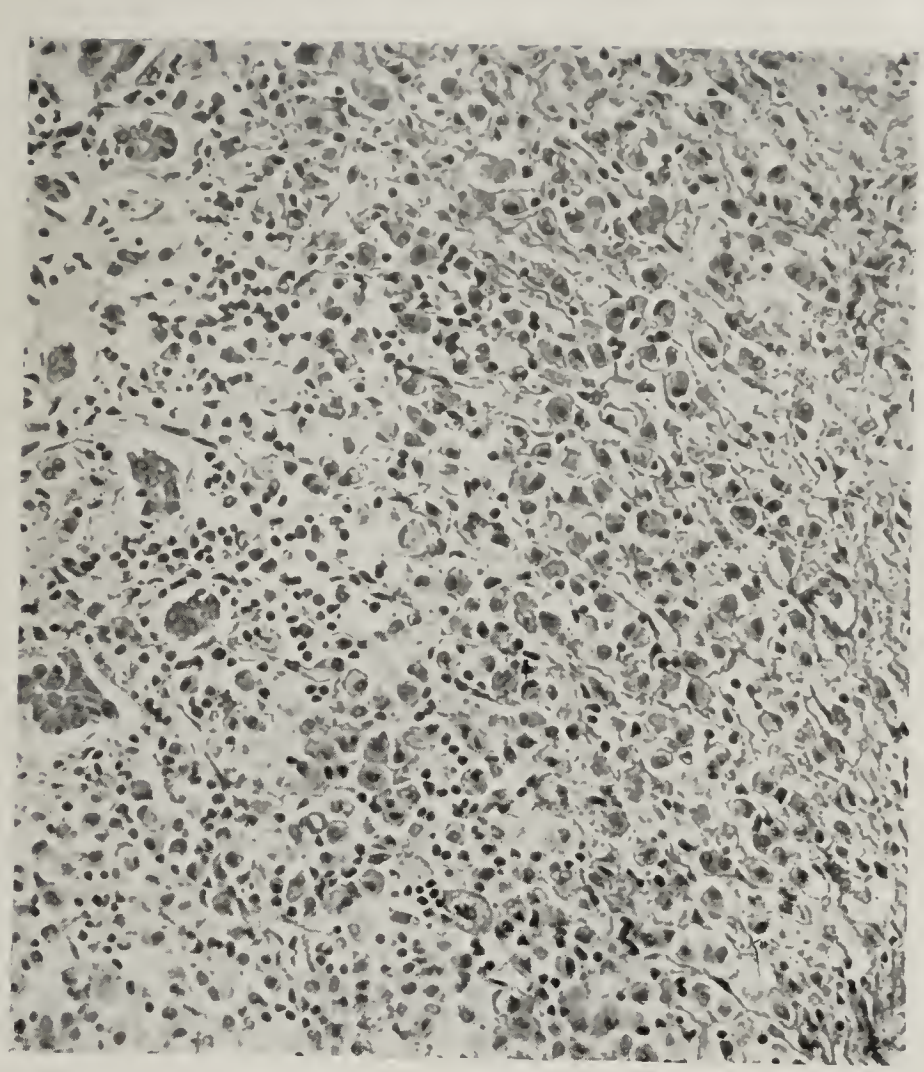

FIG. 2.—Second stage of toxic cirrhosis. Acute yellow atrophy following extensive central necrosis. Liver cells all destroyed and removed; place occupied by large numbers of endothelial leucocytes.

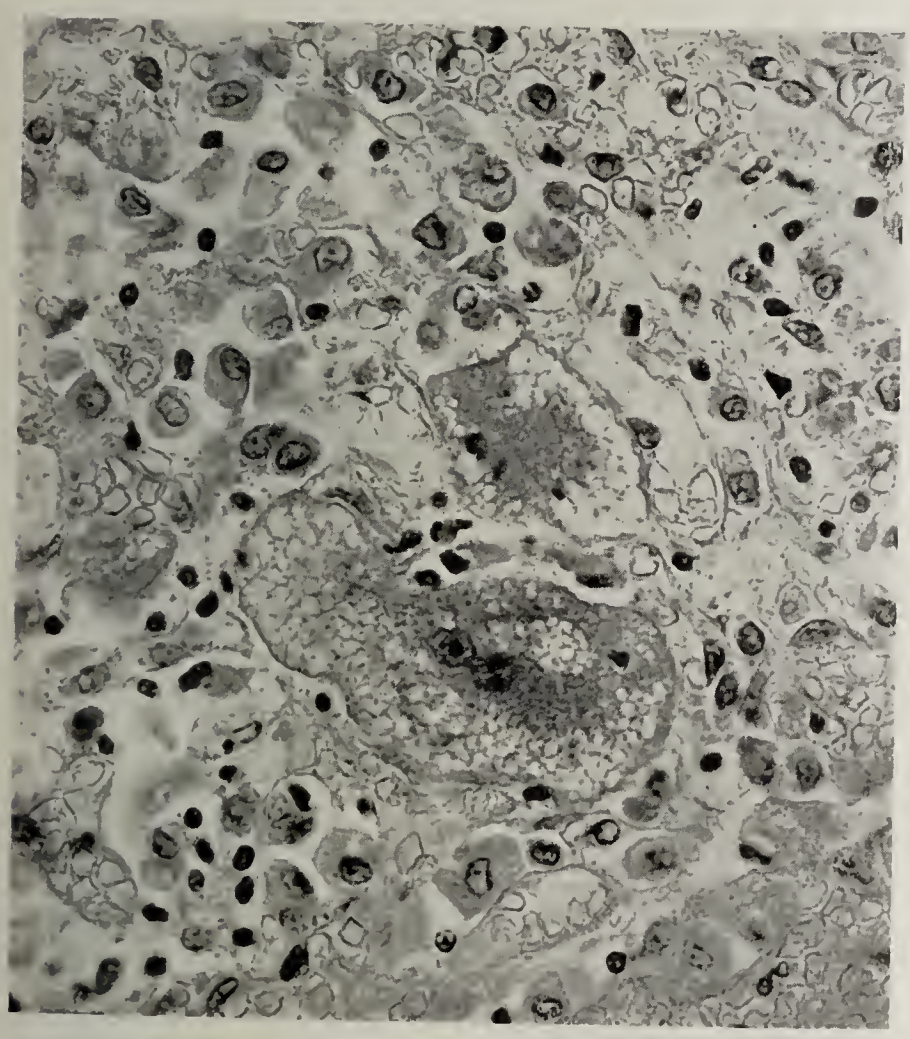

FIG. 3.—From same case as Fig. 2 showing a small group of liver cells from which regeneration may take place.

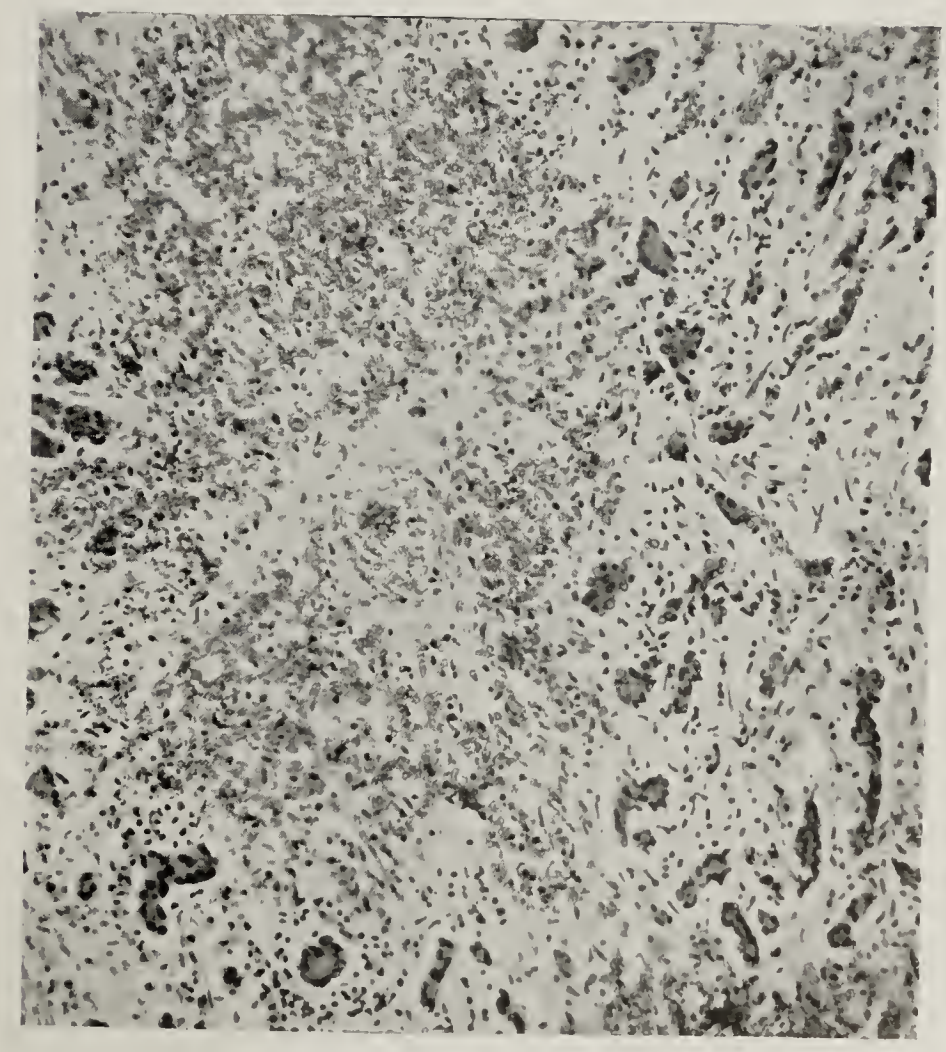

FIG. 4.—Late stage of toxic cirrhosis. Lobule of liver from acute yellow atrophy after repair has taken place No regeneration of liver cells; sinusoids filled with blood; bile ducts have extended part way towards the hepatic vein and then stopped; contraction and thickening but no increase of connective tissue.

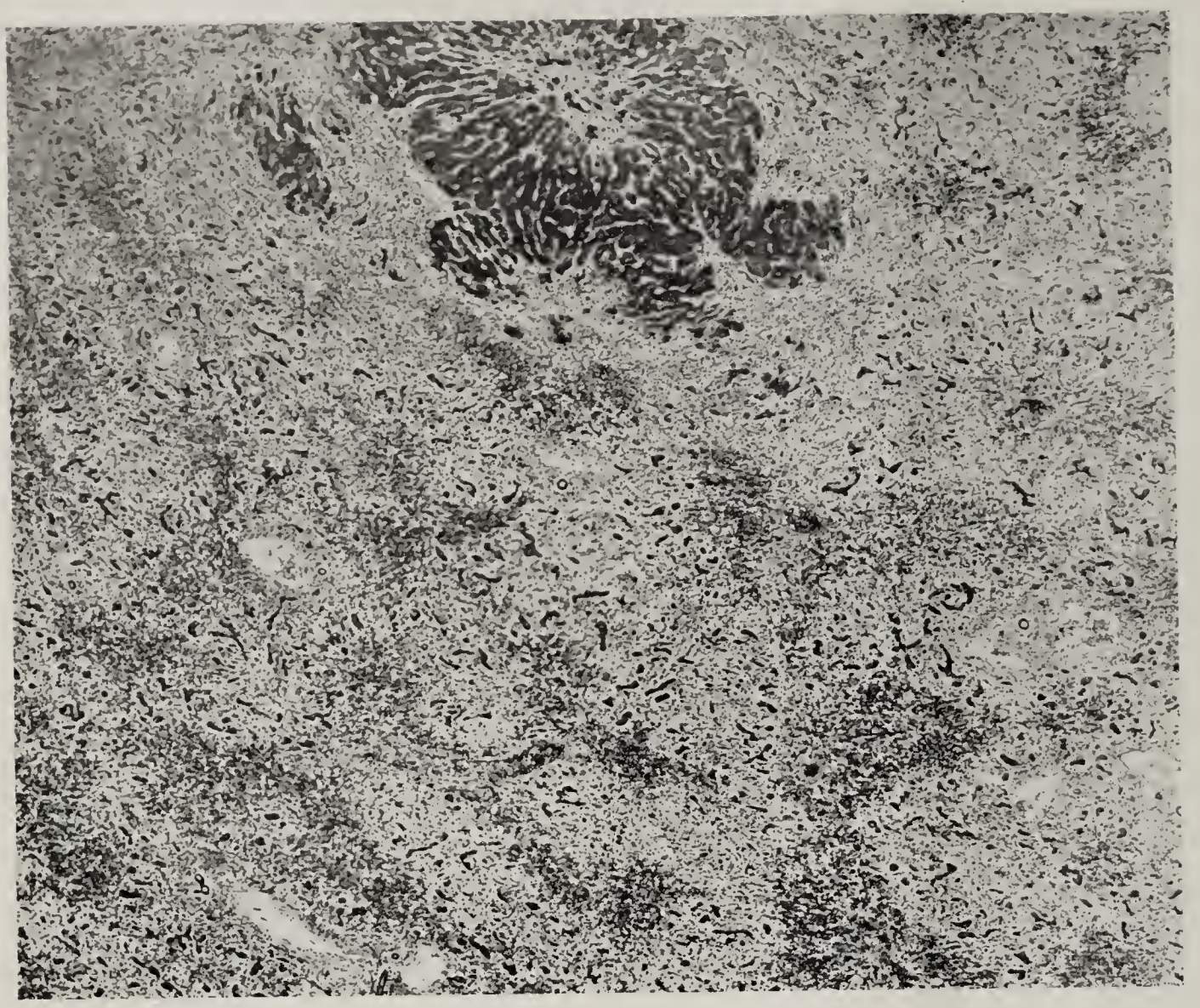

FIG. 5.—Late stage of toxic cirrhosis. Sclerosis of liver following extensive central necrosis and acute yellow atrophy. Lobular arrangement preserved but shrunken; bile ducts prominent.

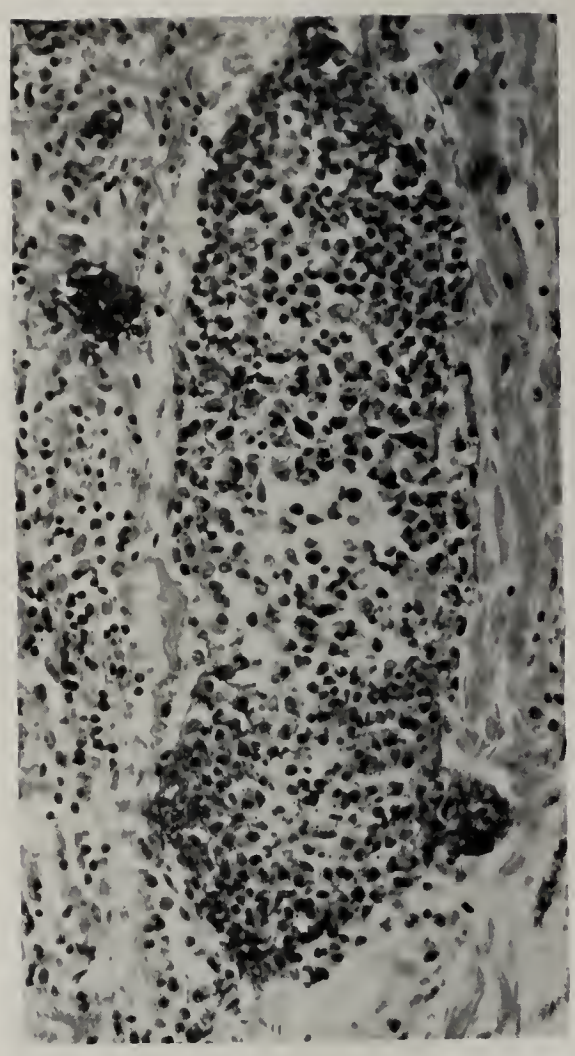

FIG. 6.—Early stage of infectious cirrhosis. Lymphatic in capsule of liver dilated and filled chiefly with endothelial leucocytes.

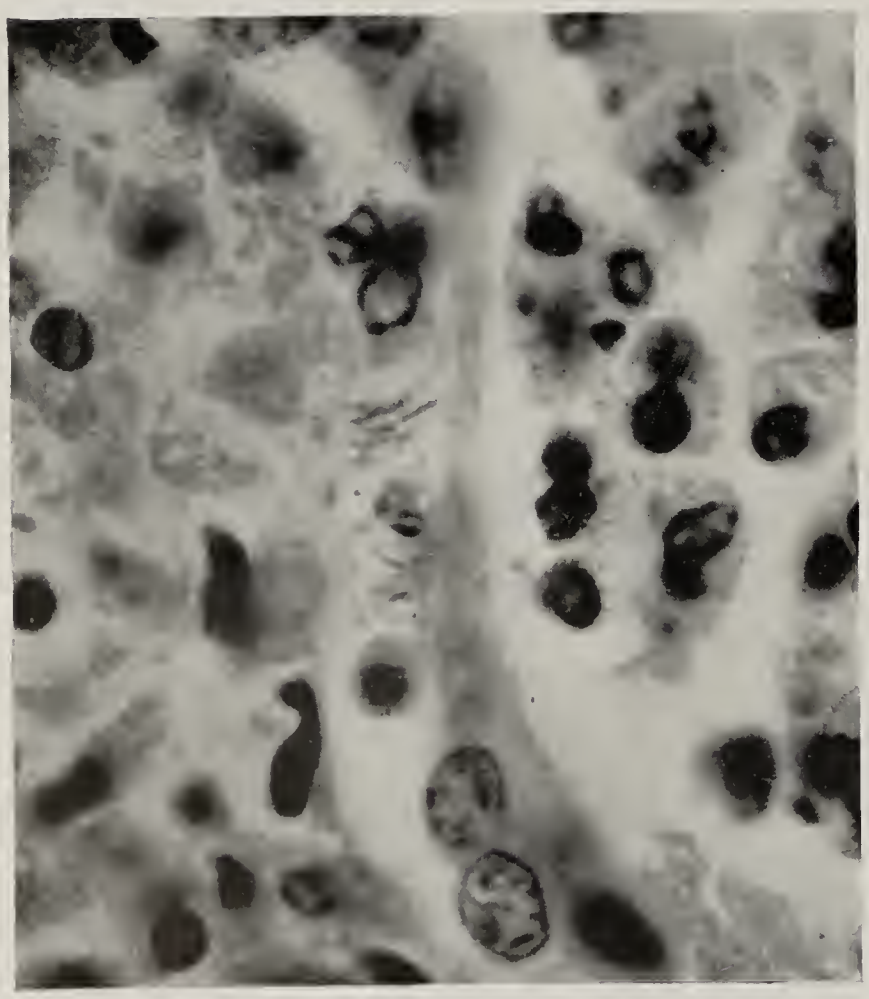

FIG. 7.—Early stage of infectious cirrhosis. Bacilli present just outside of a distended bile duct filled with leucocytes.

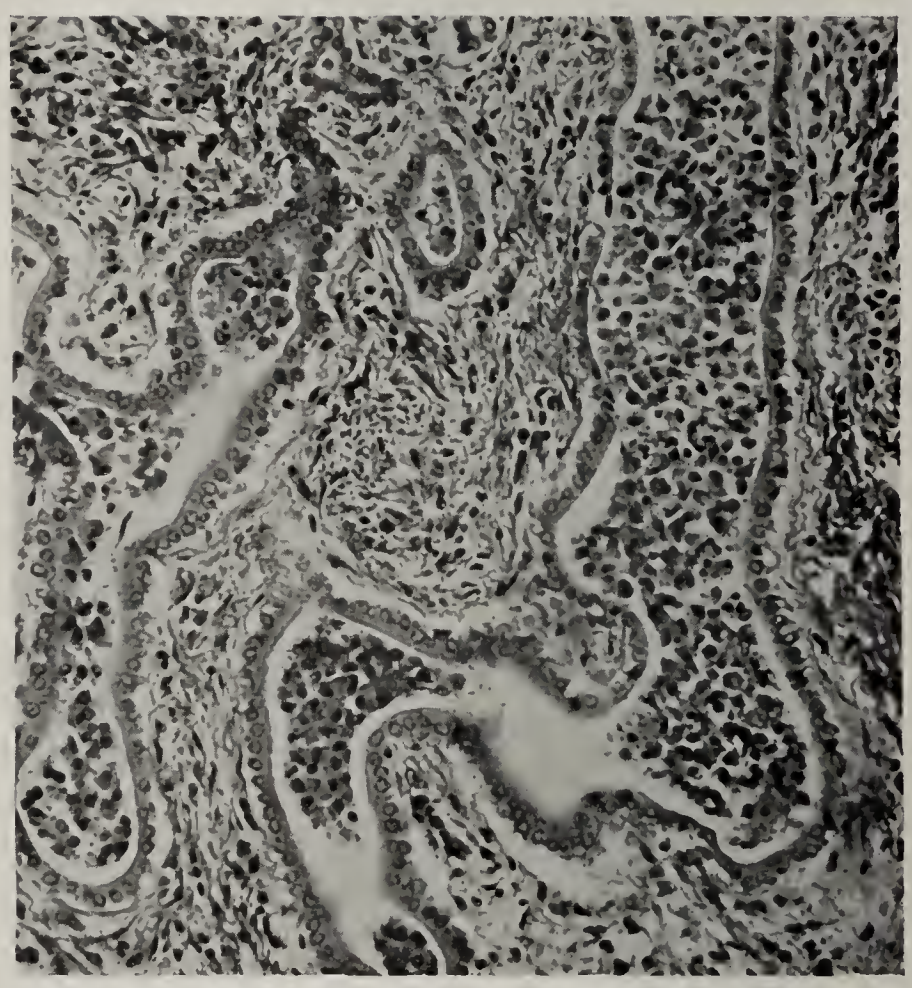

FIG. 8.—Early stage of infectious cirrhosis. Bile ducts dilated and filled with endothelial leucocytes.

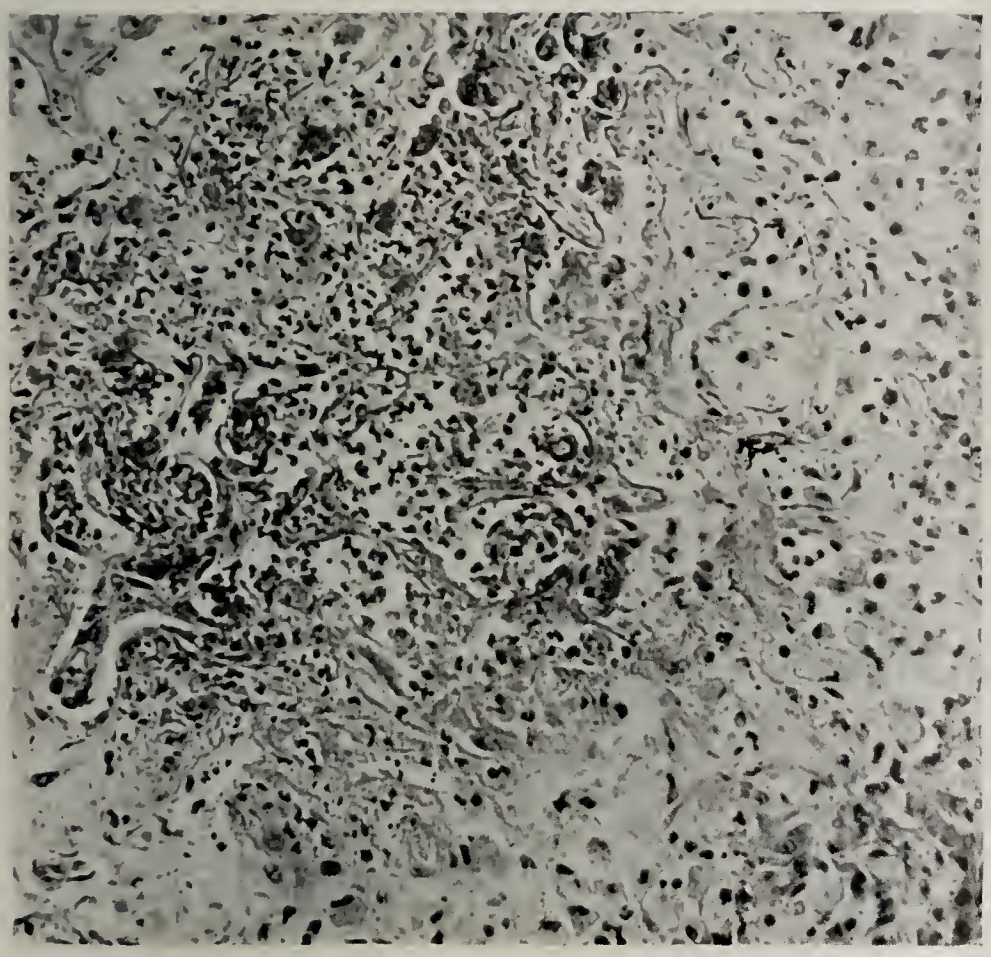

FIG. 9.—Bile stasis complicated by infection along bile ducts. Area of necrosis infiltrated by polymorphonuclear leucocytes.

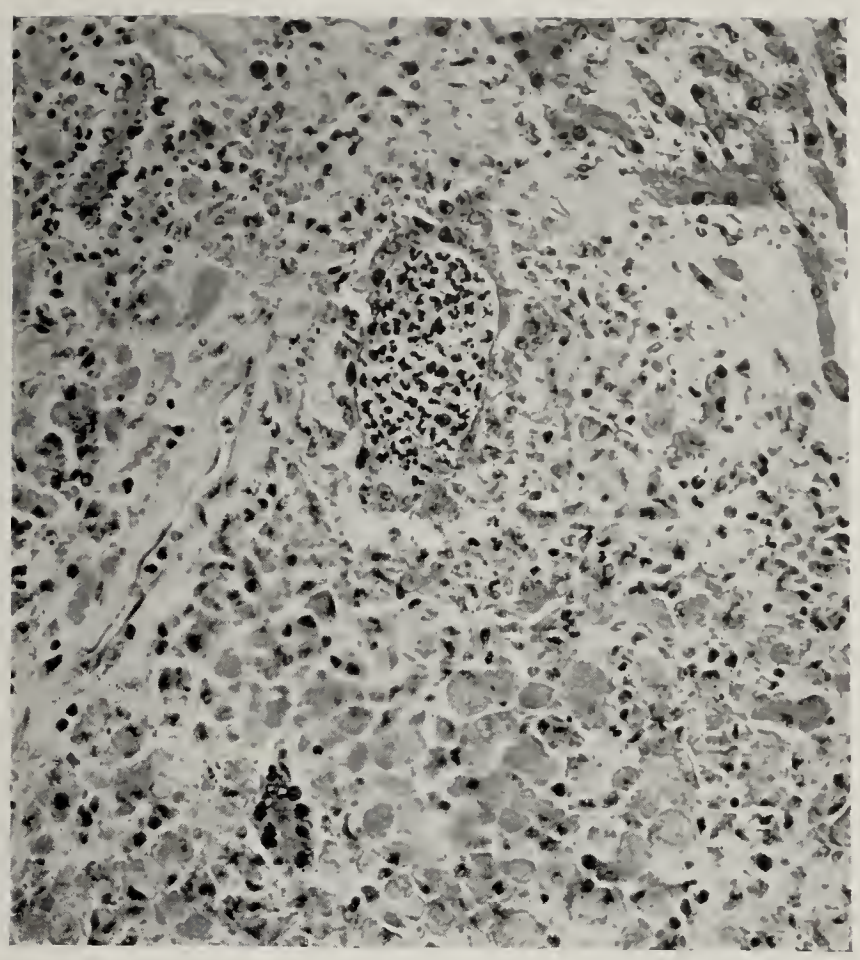

FIG. 10.—Early stage of infectious cirrhosis. Bile duct distended and filled with polymorphonuclear leucocytes; in adjoining area of softening chiefly endothelial leucocytes containing bile and fat.

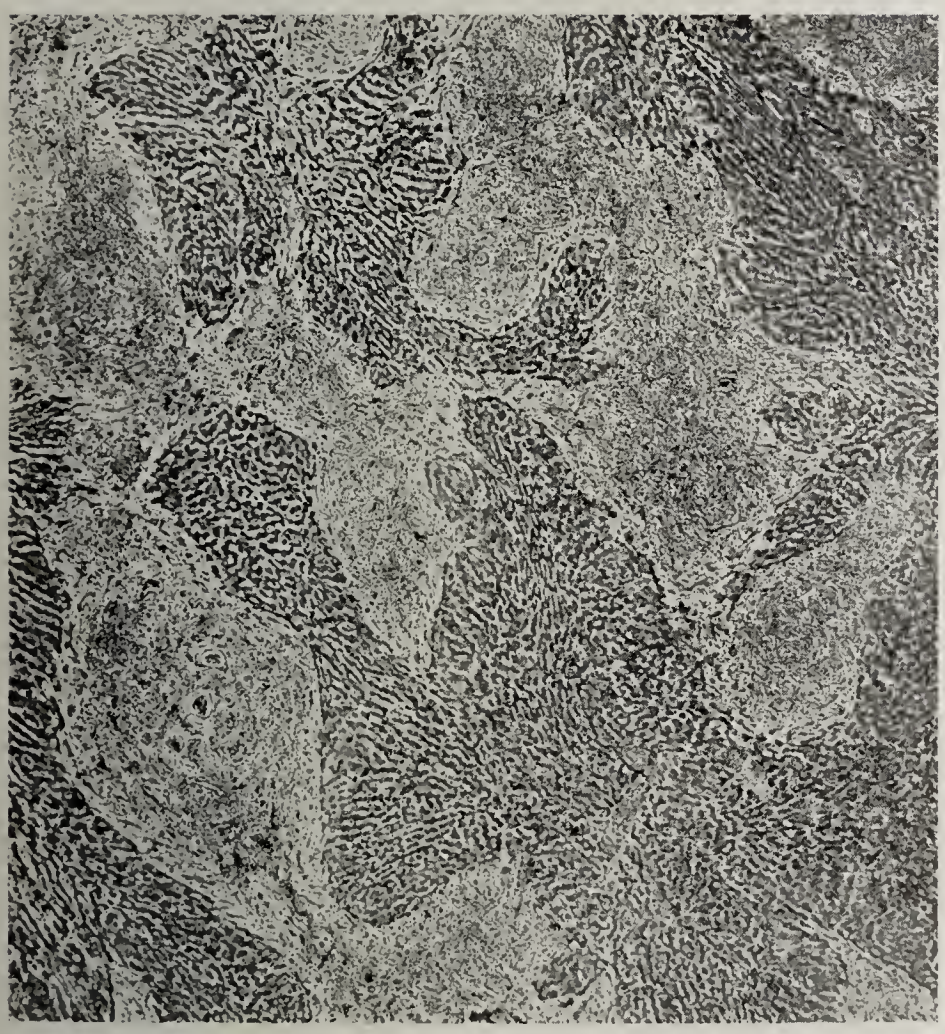

FIG. 11.—Early stage of infectious cirrhosis showing lesion situated around the portal vessels.

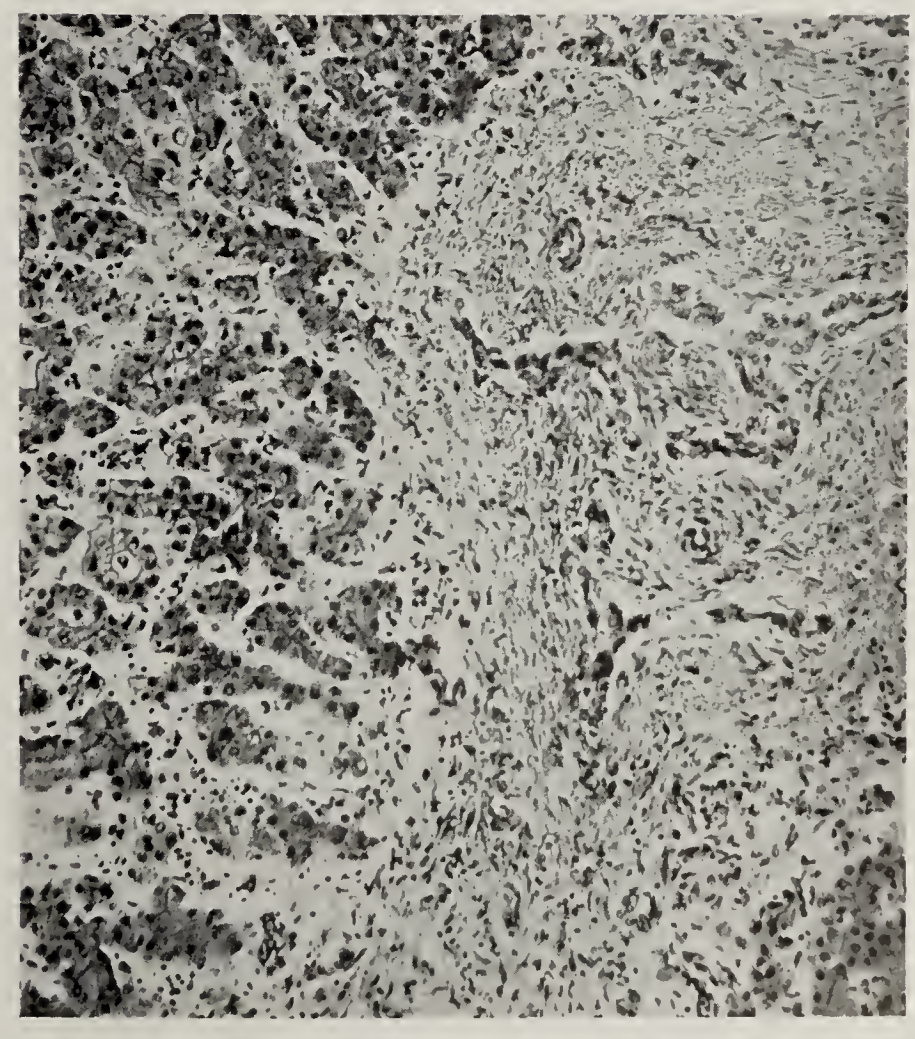

FIG. 12.—Late stage of infectious cirrhosis after repair has taken place.

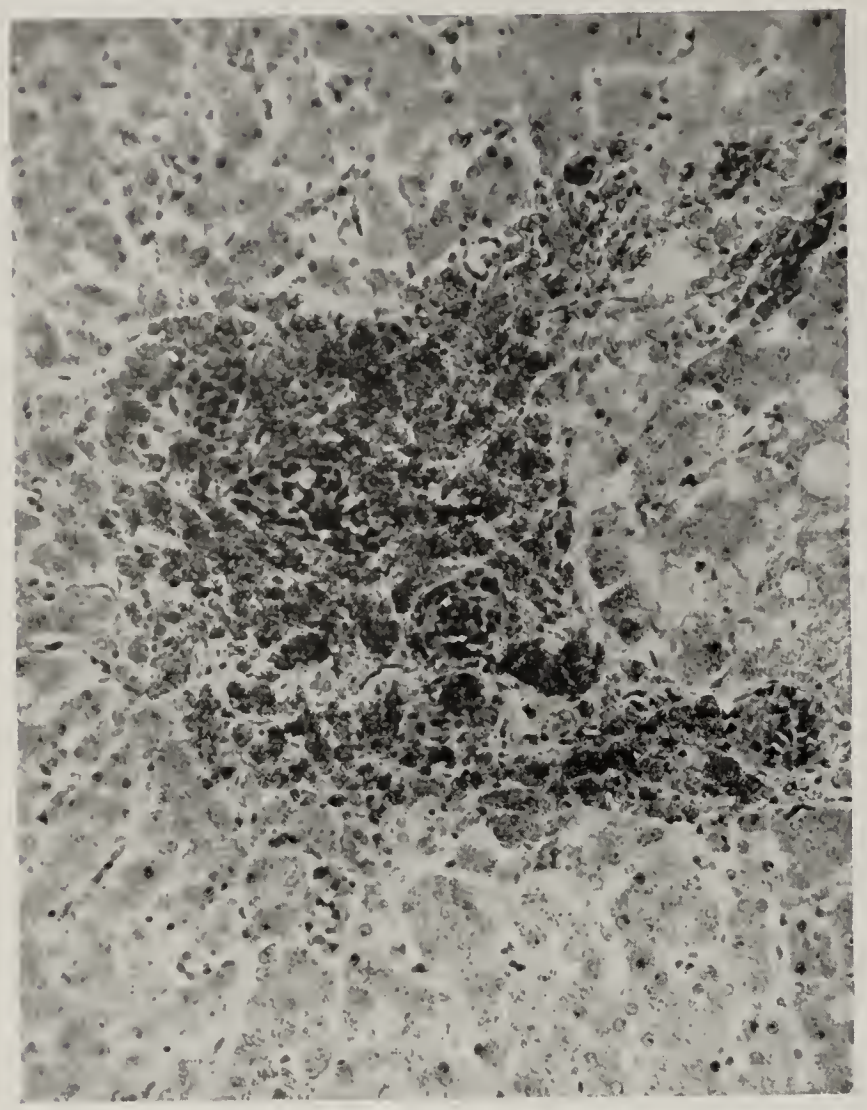

FIG. 13.—Pigment cirrhosis from a case of hæmochromatosis showing masses of endothelial leucocytes filled with blood pigment crowding the lymph spaces around the portal vessels and mechanically causing sclerosis.

FIG. 14.—Pigment cirrhosis from a severer case of hæmochromatosis showing much pigment and sclerosis.

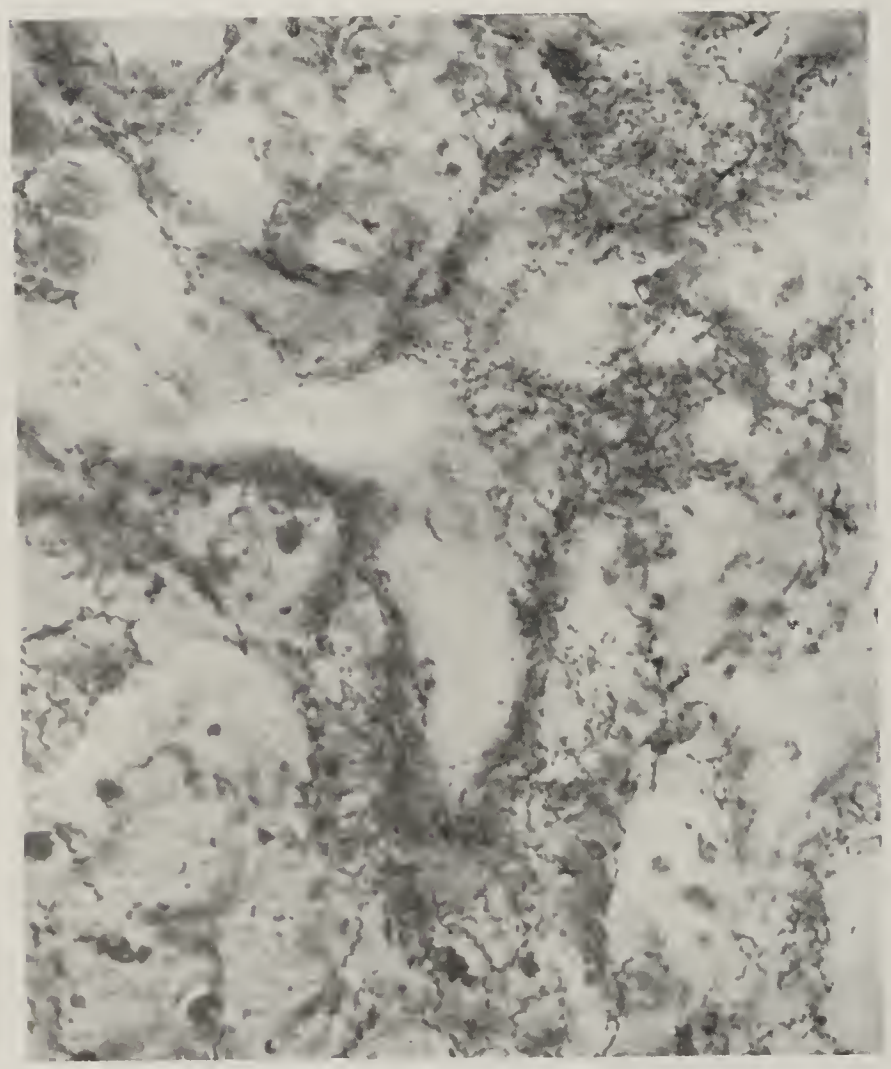

FIG. 15.—Syphilitic cirrhosis. From a case of congenital syphilis showing masses of treponemata situated in the connective tissue between the liver cells and the walls of the sinusoids.

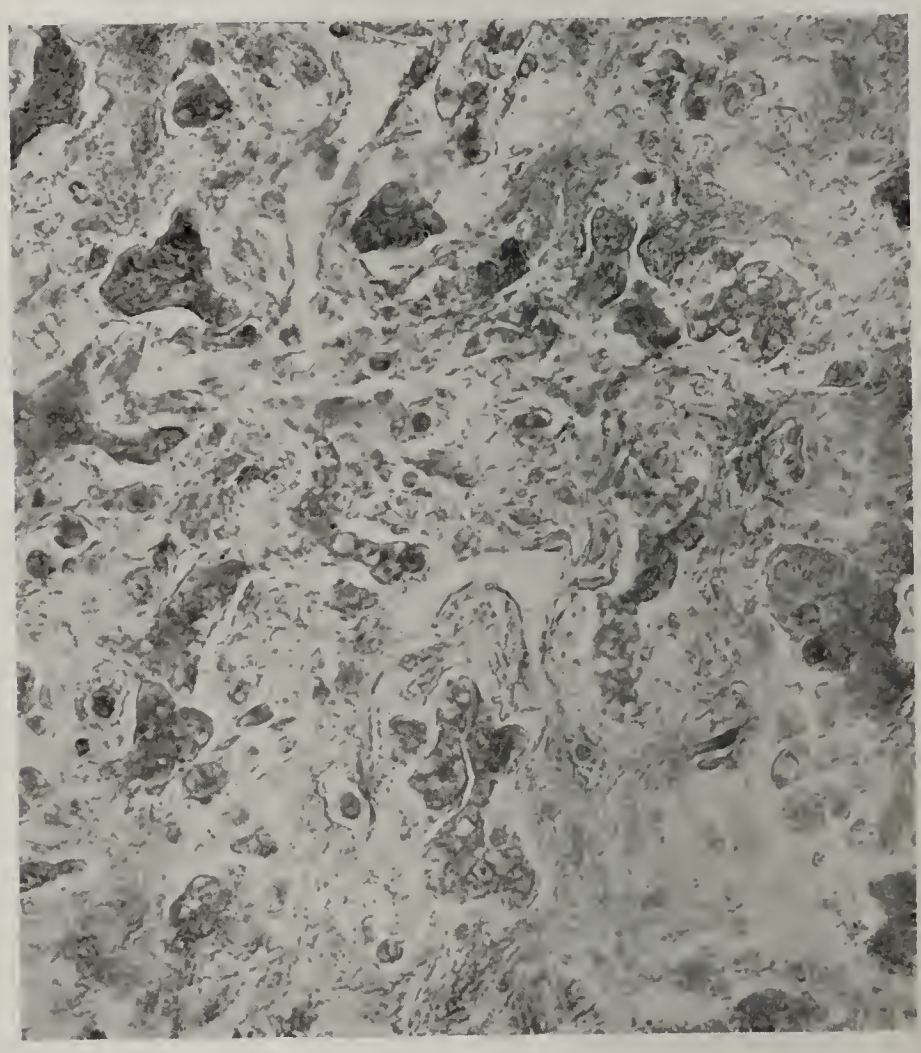

FIG. 16.—From the same liver as Fig. 15 to show the great increase of connective tissue between the liver cells and the walls of the sinusoids, which by contraction leads to compression and atrophy of the liver cells.

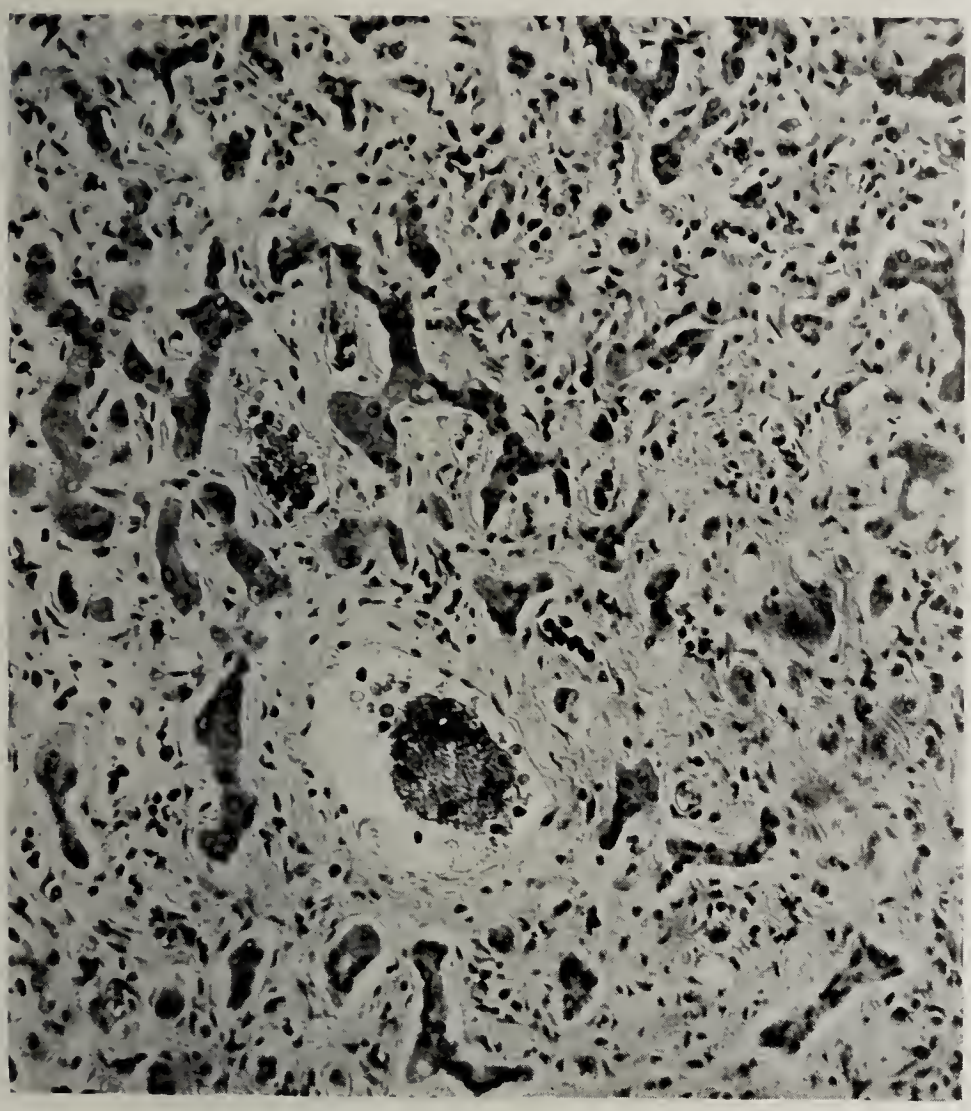

FIG. 17.—Syphilitic cirrhosis. Liver from a case of acquired syphilis in the adult showing marked diffuse increase of the connective tissue around the liver cells causing compression and atrophy of them.

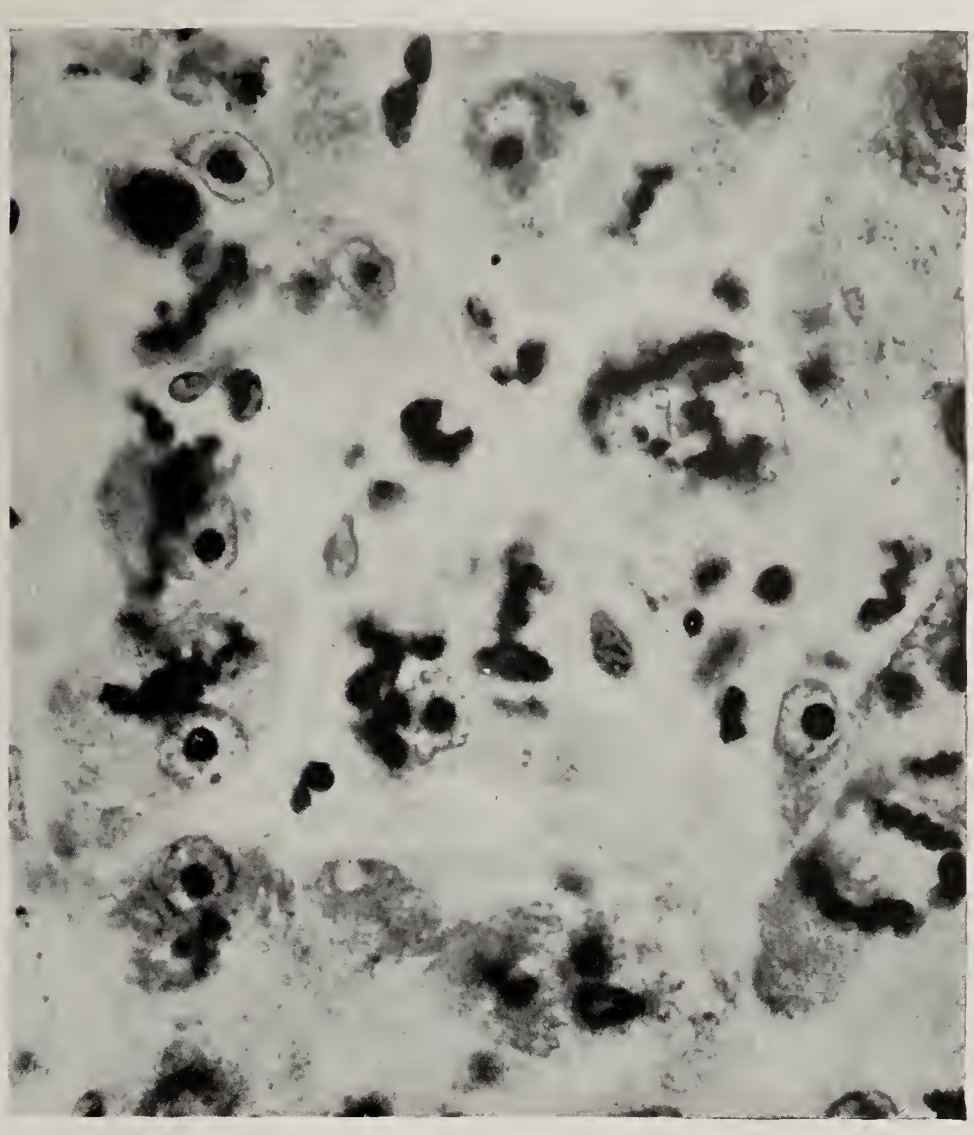

FIG. 18.—Alcoholic cirrhosis. Liver cells undergoing a peculiar hyaline degeneration before necrosis.

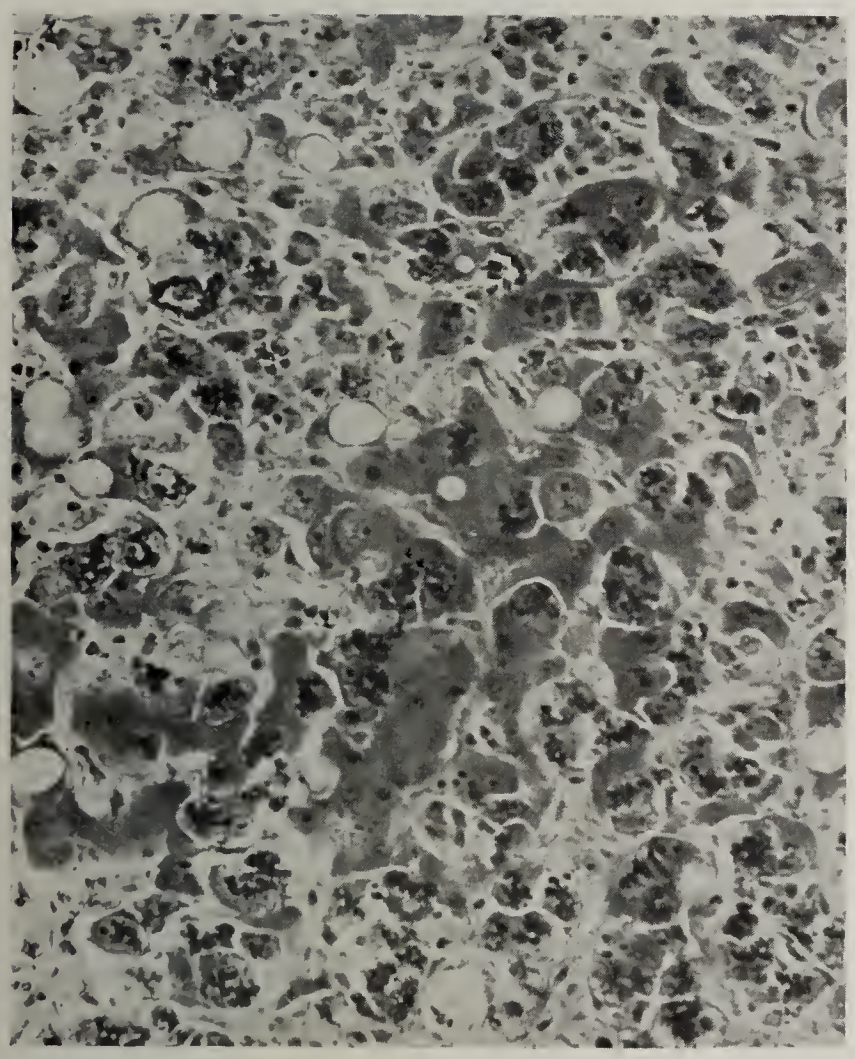

FIG. 19.—Alcoholic cirrhosis showing numerous liver cells undergoing this peculiar form of hyaline degeneration.

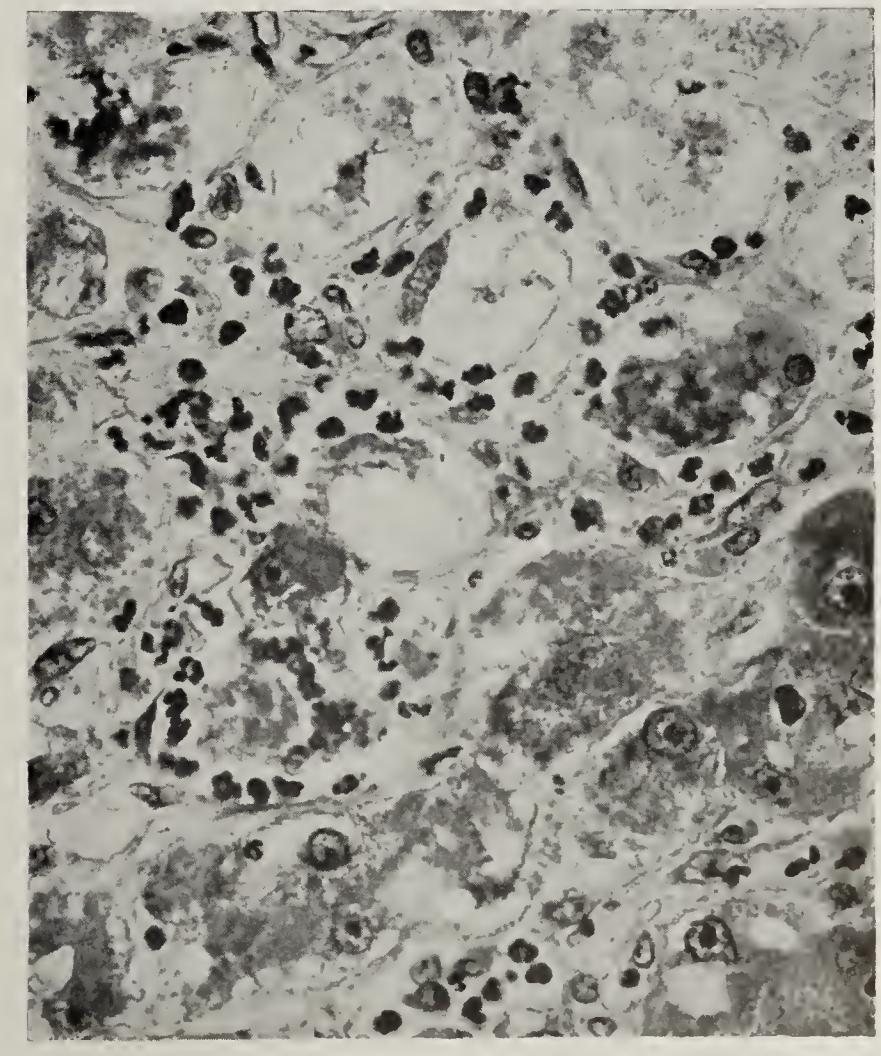

FIG. 20.—Alcoholic cirrhosis. The cells which have undergone necrosis following hyaline degeneration are being invaded by polymorphonuclear leucocytes.

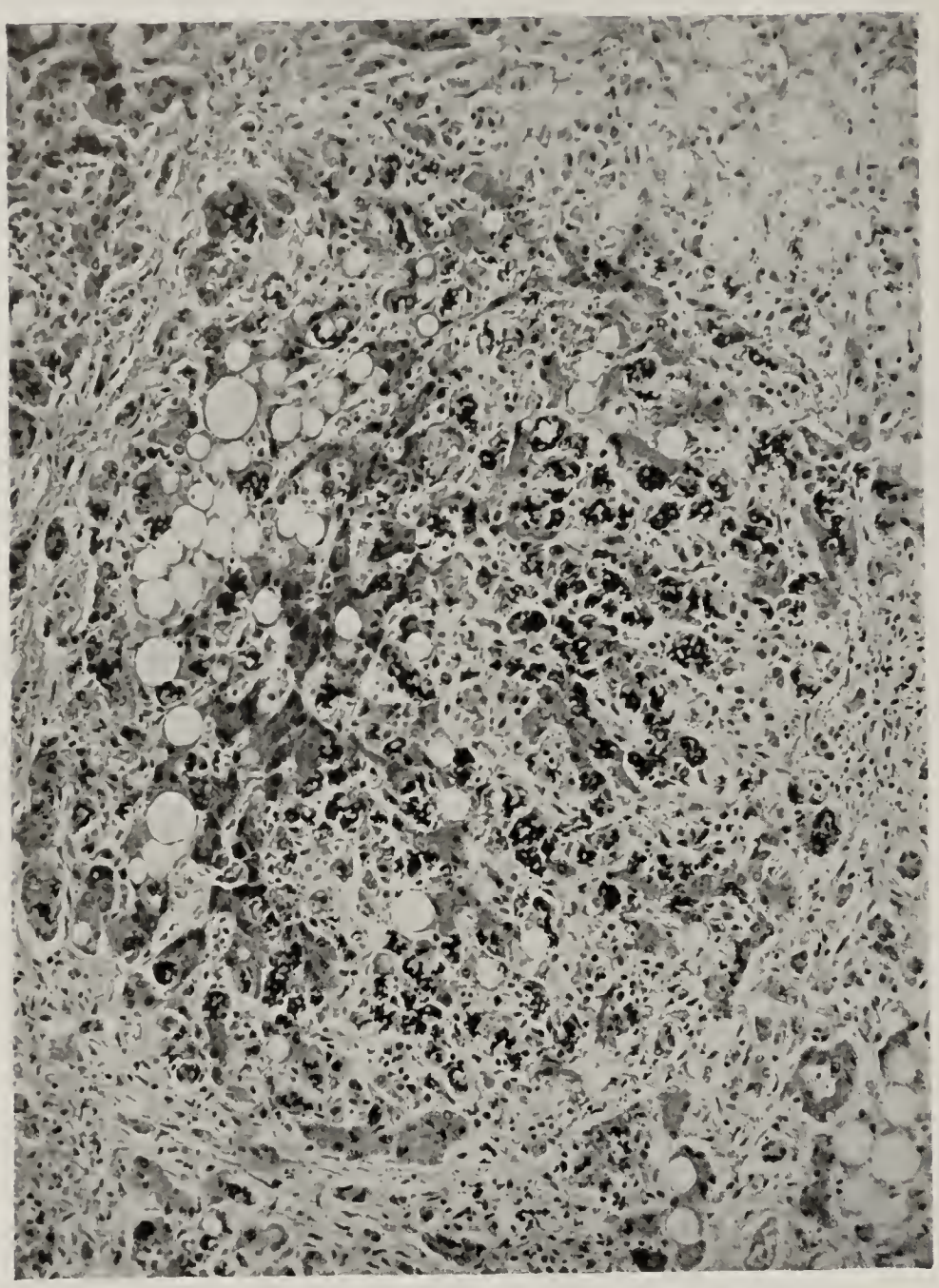

FIG. 21.—Alcoholic cirrhosis complicated with fatty infiltration.

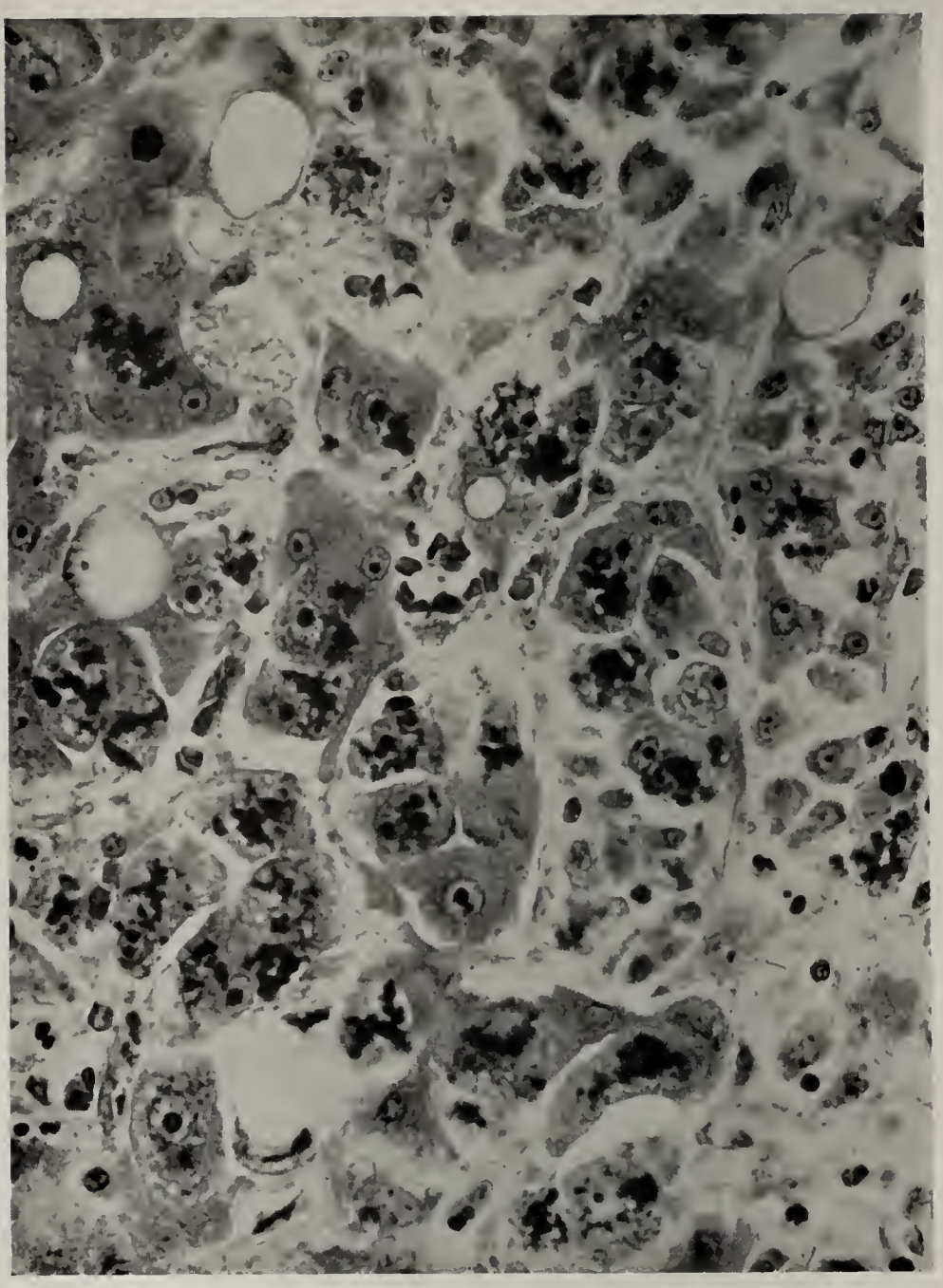

FIG. 22.—Alcoholic cirrhosis. The necrotic liver cells are being removed by the action of endothelial leucocytes.

FIG. 23.—Alcoholic cirrhosis. Compressed column of liver cells resembling a bile duct; two of the cells show the type of hyaline degeneration peculiar to the liver cells in this type of cirrhosis.

FIG. 24.—Alcoholic cirrhosis. Compressed columns of liver cells; one liver cell shows hyaline degeneration; two others contain fat vacuoles.

these compressed liver cells it is often possible to demonstrate large fat vacuoles or hyaline material due to degeneration in the cytoplasm, neither of which occurs in true bile duct epithelium.

In toxic cirrhosis the connective tissue thickens from contraction, but does not increase in amount because the fibroblasts have not been injured.

In infectious cirrhosis the fibroblasts are destroyed along with the liver cells: hence there is active regeneration and much production of connective tissue.

In syphilitic infection of the liver the primary injury is done to fibroblasts; in consequence they proliferate (regenerate), often in excess: the contraction later of the collagen fibrils produced by them results in compression and more or less atrophy of the included liver cells.

In pigment and alcoholic cirrhosis the proliferation of the fibroblasts is apparently due to injury caused mechanically by cells of exudative origin stretching the connective tissue: the reaction is similar to that produced in the lungs and peribronchial lymph nodes by endothelial leucocytes filled with carbon packing themselves in the finer lymph spaces.

For the drawings I am indebted to Miss Etta R. Piotti; for the photomicrographs numbered 7, 13, and 18 to Dr. S. B. Wolbach; for the others to Mr. L. S. Brown, of the Massachusetts General Hospital.

TYPHOID SPINE; WITH THE REPORT OF TWO ADDITIONAL CASES WITH BONY CHANGES IN THE VERTEBRÆ.

By Thomas McCrae, M. D., F. R. C. P.,

Associate Professor of Medicine and Clinical Therapeutics, the Johns Hopkins University.

The essential character of the condition termed "typhoid spine" has been the subject of much controversy but the findings of recent years have settled the question in favor of definite organic changes—a spondylitis—as against a neurosis. In 1906 the writer [1] reported two cases of typhoid spine in which the occurrence of bony changes in the vertebræ was proved by the skiagrams. At that time, while the occurrence of bony changes in the form of kyphosis, etc., had been noted, there had not been any report of bony changes as shown by skiagrams. Since then several such cases have been reported and in the present paper two additional ones are described.

Case 1. *Typhoid fever in Nov.*, 1908; *tetany (?); recovery; discharged Jan.* 8, 1909. *Symptoms of typhoid spine, March* 15, 1909. *Second admission Apr.* 17, 1909. *Second attack (relapse?) of typhoid fever Apr.* 26, 1909; *recovery.*

The patient was a white male, aged 45 years, by occupation a laborer. His family history was negative and in his personal history the only illness was an attack of malaria in July, 1908. He had formerly been a very heavy drinker but had taken no alcohol for six months before admission. *First admission, Nov.* 9, 1908. The present illness began with headache, weakness, anorexia and general malaise. Apparently at times he had been slightly delirious as there was a history of his wandering about the house in an aimless way. He was admitted on the sixth day of the disease. On admission the tongue was coated; some râles were heard over both lungs; the heart was clear. There were fairly numerous rose spots on the chest and abdomen and the spleen was palpable. A blood culture gave typhoid bacilli, and the Widal reaction was positive on the day of admission and again on the 16th day. The patient showed signs of marked toxæmia, but the only feature of special interest was the occurrence of a condition much like tetany during the course of the disease. There was marked flexion of the toes and the hand was held in the position seen in tetany, this becoming much more marked when the cuff of the blood pressure apparatus was applied to the upper arm. The temperature became normal on the 37th day of the attack and the patient was discharged in good condition on Jan. 8, 1909. During his convalescence there was no complaint of any pain or discomfort in the back and he felt well on leaving the hospital.

[1] Am. J. Med. Sc., 1906, CXXXII, 878.

Second Admission—April 17, 1909.—After discharge from the hospital he did not return to work until Jan. 30, when he resumed his occupation in the blacksmith department of the works where he was employed. This involved some heavy lifting but he was quite sure that there had not been any injury or strain. He felt perfectly well until March 15, when he began to have pain in the lower part of the back; there was no other symptom. The onset was gradual and he was able to continue at work for one week but then had to give up on account of the severity of the pain. This was not constant but came on in paroxysms which lasted from 15 to 20 minutes. The patient commented on the effect on his general condition, remarking that the pain had made him "weak and discouraged." He emphasized the fact that the pain was much worse in the night than during the day and attributed his feeling so badly to loss of sleep rather than to the pain.

Examination.—The patient's general condition was good. The lungs were clear throughout except for a few râles at the bases. The heart was slightly increased in size, the impulse being feeble; the sounds were rather distant and the first had a slight murmurish quality at the apex. The pulse was of fair volume and the blood pressure 110 mm. Hg. The abdomen was negative; no rose spots were seen and the spleen was not felt. The abdominal walls were soft; there was no contraction of the muscles. The hæmoglobin was 86 per cent, red cells 5,100,000 and leucocytes 5700 per cmm. When the patient stood up there was a rather well marked scoliosis in the lumbar region and the right shoulder was held higher than the left. The usual lumbar lordosis was almost obliterated. There was very little movement of the lower spine when the patient bent forward and to the left or right and there was practically no movement in the lower spine when he bent backward. The spine showed very little movement below the tenth thoracic vertebra. On palpation there was some tenderness on both sides of the lumbar spine but no tenderness on pressure over the spinous processes of the vertebræ. The muscles on both sides were contracted and stood out prominently, this being more marked on the right side. The knee jerks and tendo Achillis reflexes were rather more active than normal and equal on the two sides, but the arm reflexes showed much the same increase. There was a normal response to plantar stimulation. At this time the patient had slight fever, about 100° F., which disappeared in the next three or four days. For the next five days the condition was practically the same. There was slight tenderness on pressure over the lower spines, especially about the fourth

lumbar vertebra, and distinct tenderness on either side especially to the left of the fourth and fifth lumbar vertebræ. As long as the patient made no movement he was fairly comfortable but when asked to stand on his toes and come down forcibly on the heels he did this very slowly and carefully. When he walked the back was held very stiffly and when he tried to get out of bed he had great difficulty in doing it, the back being held rigidly and the patient bracing himself as much as possible by the arms. The abdominal muscles at times were held very rigidly. When the patient was flat in bed the lumbar lordosis seemed to be obliterated and there was marked rigidity of the muscles on both sides of the spine in this region. The *X-ray plate* on April 22d showed marked ossification of both lateral ligaments in the lumbar region and also a suggestion of this in the anterior ligament (Dr. Baetjer).

About this time for a period of two days, the patient was unable to void urine and he had to be catheterized. On April 23d the temperature rose to 100° F., and the next day to 103° F., which proved to be the beginning of a typical attack of typhoid fever. A blood culture on April 26 (the fourth day of the fever), yielded typhoid bacilli and the Widal reaction was also positive. On April 27, it was noted that the spleen was enlarged and palpable. No rose spots were made out. During the illness the patient suffered greatly from the pain in the back, at times this being extremely severe. His expression of apprehension when anyone came near the bed, fearing that they might touch it and so cause him pain, was always striking. He looked very haggard and ill, and remained absolutely motionless unless he had to move; this was done with great deliberation and care and there was no doubt of the severity of the pain. Examination showed no disturbance of sensation in the legs; ordinary sensation, pain and temperature sense all seemed normal. The attack of fever was not very severe; the patient did well and the temperature reached normal on May 8, the 16th day of the attack or relapse. The blood count showed a slight drop, as the hæmoglobin was 80 per cent, red cells 4,460,000 and the leucocytes 6800 per cmm. The leucocyte counts throughout were between 6000 and 7000. The urine showed a specific gravity usually between 1014 and 1028; there was no albumin or sugar. A positive diazo reaction was given once. The blood pressure was low, generally between 80 and 100 mm. Hg., averaging about 90 mm. Hg.

On May 20, a plaster cast was put on with the patient in a hammock. A second one was applied a week later and the patient was much more comfortable. At this time he complained very little of pain and got about without much difficulty. There was no evidence of any wasting in the legs more than is usual after an attack of typhoid fever. The leg reflexes were rather active but equal on the two sides and sensation seemed perfectly normal. The X-ray plate showed the same changes in the vertebræ as before. He was discharged in good condition on June 8.

On July 18, 1909, the patient was seen and found to have been improving slowly. He had not returned to his usual employment but had been doing a certain amount of light work which did not involve much exertion. He had been wearing a plaster jacket and stated that he suffered very little from pain in the back although he had felt weak. Two days before this examination he removed the plaster jacket and since then has had rather more pain. Examination of the back did not show any change in the spine but the muscles on the right side were still definitely more contracted than on the left. There was no kyphosis and no definite scoliosis. What pain the patient had was referred to the lumbar region but there was no tenderness on pressure over the spine. The reflexes in the legs were still much exaggerated. Four months later he was practically well.

Remarks.—One point of interest is the occurrence of a relapse or second attack between five and six months after the original attack. Whether this should be termed a relapse or a second attack is difficult to decide, for there is no period which can be set as a dividing line between a relapse and a second attack. The case here reported is much like one previously described by the writer,[2] in which the original attack began on June 2, the patient being convalescent in March when the symptoms of typhoid spine appeared. He was admitted to the hospital on July 4 of the same year for the spinal symptoms, and a week later the second attack (or relapse) of typhoid fever began. In both these cases there was an interval of months between the attacks, in which the symptoms of spondylitis appeared. One explanation of the cause of typhoid spondylitis is that there are local lesions in the bone in which typhoid bacilli are present. It is tempting to suggest that this focus may have been the source of the second infection in these cases. However, our knowledge of what determines relapses is not very satisfactory and it would be easier to regard the second febrile attack in these two cases as a second attack rather than as a relapse. Besides the retention of typhoid bacilli in the body after recovery from an attack of typhoid fever is so common (e. g. in the gall bladder) that we should not attach too much importance to such a source of reinfection.

Case 2. *Typhoid Fever in June*, 1909; *intestinal hemorrhage; phlebitis; recovery; discharged Aug.* 14, 1909. *In October*, 1909, *neuritis of the right external popliteal nerve; spondylitis found.*

The patient was a white male, aged 45, whose occupation was a worker in a factory in which he did a great deal of heavy lifting. The *first admission* (Medical No. 24248) was on June 14, 1909, when he came complaining of cough. There was no history of arthritis and he had not used alcohol. He had always been a hard worker and a heavy eater. His illness began eight days before admission when he received a severe wetting. For a day or two after this he felt dizzy and had some indefinite trouble in the head; this was much worse after he spent some hours working in a hot room. There was also some headache and indefinite pains about the chest. On examination the patient was a healthy looking man with a good color. The percussion note over the lungs was rather hyperresonant and there were a few râles heard on both sides of the chest; the heart was clear. The abdomen was natural; no rose spots were found and the spleen was not felt. Four days after admission the temperature fell to normal and then rose again, at one time reaching 105° F. Definite rose spots appeared and there was slight jaundice. On June 22, about the 16th day of the illness, the patient passed blood from the bowel, but the hemorrhage was not severe, and made no change in the patient's general condition. On June 21, the 15th day of the disease, the blood culture was positive, typhoid bacilli being obtained. The course was without any special features till he began to get up out of bed on August 8, when he complained of some pain in the right leg, both in the popliteal space and below the knee. The leg was somewhat swollen below the knee; the skin had a shiny appearance and was quite sensitive to the touch. There was definite swelling and the circumference of the right calf was 3 cm. greater than the left. This was regarded as a mild attack of phlebitis and subsided before discharge on August 14th.

For a time after leaving the hospital both legs were very weak, especially below the knees and the swelling and pain in the right leg returned after discharge. In from two to three weeks the weakness of the left leg had disappeared entirely but the right

[2] *Loc. cit.*

leg did not improve as rapidly and it was only after a period of about six weeks that the pain and swelling in the right leg disappeared and the patient was able to walk about without any special discomfort. During October the patient was seen several times in the out-patient department. His complaint was especially of dizziness and weakness, but he stated that he had not suffered from any pain. He had chronic ear trouble for which he had been treated some time before and the aurist considered that this was possibly responsible for the dizziness. The patient had made several attempts to resume work but found that he had not sufficient strength and that when he went to do any heavy lifting he was apt to stagger. It was not possible to obtain the history of any special strain or injury during this time and no definite evidence of spondylitis could be found although the patient was repeatedly examined with this in mind. There had not been any pain in the back and it was difficult to test the movements of the spine as on any attempt at bending the patient complained of dizziness and was afraid of falling. In the absence of any definite symptoms suggesting spondylitis it was not thought necessary at this time to have an X-ray plate taken. During this time he had gained twenty pounds in weight and was a good deal stronger.

Towards the end of October the patient began to complain of trouble in the right foot. He stated that at first there was numbness over the upper part of the foot and especially in the great toe; later he had some difficulty in walking as he was unable to properly lift the foot. On October 27, it was found that he had some difficulty in walking and that the right foot dragged a little. A few days later he complained of a good deal of pain in the right foot, and the gait was distinctly more affected. The knee jerks were present on both sides but the ankle jerk was decreased on the right. He had no power of movement in the right great toe and had difficulty in lifting the foot. In view of the condition he was admitted to the hospital November 9. (*Second admission*). On examination the patient's general condition was excellent; the lungs and heart were clear throughout. The abdomen was normal and the spleen was not felt. On examination of the legs it was found that there was marked foot drop on the right side with marked weakness of the extensors of the right foot. Voluntary dorsal flexion of the right foot was possible but the right great toe could not be flexed or extended except that slight flexion occurred when the other toes were moved. Passive movement of the great toe was possible in any direction. The knee jerk on the right side was much more marked than on the left. Plantar response was normal on the left side but could not be obtained on the right side. There was no ankle or patellar clonus. The superficial veins of the right leg were definitely dilated but there was no œdema of the feet or ankles, and well-marked pulsation was present in the dorsalis pedis artery on both sides.

Over the dorsum of the right foot, from the ankle along the mesial margin, including the right great toe and extending to the tendon of the extensor digitorum longus, sensation to touch was much affected and the response to pain and temperature stimuli was rather inaccurate. Along the medial border there was an area of hyperæsthesia; pain stimuli caused a marked contraction of the rectus femoris, almost approaching a spasm. There was no atrophy of the calf muscles and there did not seem to be any difference in the strength of the hamstring muscles of the two legs. The sensory disturbances cleared rapidly and disappeared by November 25. On electrical examination it was found that with the galvanic current the affected nerve did not respond to stimuli; the muscle itself responded to a strong current, the ccc. being stronger than the acc. With the faradic current the nerve did not respond; the muscle responded sluggishly and less so than the muscle on the other side.

The *X-ray plate* by Dr. Baetjer showed a definite deposit of bone on the left side of the spine between the articulations of the III, IV, and V lumbar vertebræ, which practically obscured the articulations. The bone was deposited on the lateral ligaments and the anterior and posterior ligaments seemed free. There was no deposit on the right side.

During this time the patient's temperature was practically normal, and he was discharged much improved after being ten days in the hospital. The patient's condition improved steadily after this and in January, 1910, the signs in the right leg had practically disappeared. He complained that the right leg tired more quickly than the left; this may have been due as much to the effects of the phlebitis as to the paralysis. By the beginning of March the patient seemed perfectly well. He did not make any complaint of pain in the back and the movements of the spine seemed normal except for slight limitation in the lumbar region. He had returned to work and seemed able to do this without difficulty.

Remarks.—This case is unusual in several particulars. In the first place it shows that typhoid spondylitis may occur without any severe pain. The symptom of pain has been regarded as the most essential one in "typhoid spine" and it is very evident in this case that but for the radiogram the diagnosis of spondylitis could not have been made. In this event the condition in the popliteal nerve would have been regarded as a post-typhoid neuritis and the causal influence of the local process in the spine would not have been recognized. The involvement of the nerve root on the opposite side to that on which the deposit of bone occurred is seen not infrequently in cases of spondylitis.

The Nature of "Typhoid Spine."—Formerly the term was applied to a symptom picture regarded by many as being a neurosis in the majority of cases. That it may be a neurosis in some cases is quite possible but the increase in our knowledge of the organic changes which occur in "typhoid spine" speaks against this view. This is upheld by the fact that as the condition was studied more carefully an increasing number of cases have been reported with evidence of definite bony changes, supporting more and more strongly the view that it is a spondylitis. This is analogous to the change in our views regarding spondylitis generally. The work of recent years has shown that many of the cases formerly regarded as lumbago, "rheumatism," etc., are instances of spondylitis, probably associated with various organisms in different cases. The proportion of cases of "typhoid spine" with bony deformity or shown by the X-rays to have bony changes is comparatively large, in fact as large as could be expected. Spondylitis is of very varying degree in different cases and many of those which we see with other conditions—such as arthritis deformans when a spondylitis is part of a multiple arthritis—give no positive evidence of bony changes either by deformity or by the X-rays.

In 1907 Silver [3] collected 67 cases of typhoid spine of which 14 were rejected for various reasons, leaving 53 fairly definite cases. Among 51 of these in which the sex was stated only six

[3] Typhoid Spine; a report of a case with radiographic evidence of structural change; analysis of the reported cases; complete bibliography." The Am. J. Orthop. Surg., 1908, V, p. 194. In the same volume is an article by Myers, "Typhoid Spine with special reference to the deformity." These are two interesting and comprehensive articles which should be read by all interested in the subject.

were females. In making this collection Silver exeluded those eases in which a neurosis seemed probable. Myers found in his study that kyphosis had been notieed in 36 per cent of the eases. It seems a fair inference that in a large number of cases with an actual spondylitis this need not proceed to the extent of eausing external bony change. However, the number of cases with external bony deformity, considered with the number in whieh radiographs show bony changes, points to the probability that the symptoms are due to a definite process in the spine or its attachments. To deeide this question as far as possible the various changes which suggest definite local changes may be considered.

1. *Local swelling.*—This has been frequently noted and Silver found it reportcd in 14 (26 per cent) of his colleeted series. Redness has been present in a few cases, tenderness in many more, sometimes over the spine, sometimes over the adjaeent muscles. Rigidity of the spine has been quite common and may be considered to be almost invariably present.

2. *Changes in the spine.*—Kyphosis was noted in 15 of his series by Silver and by Myers in 20 of 56 cases (36 per cent). The descriptions of this vary considerably but it is fair to say that some degree was present in one-third of the eases. Seoliosis was noted in some cases, in nearly all of whieh it disappeared after an interval. Alteration of the lumbar curve is not uncommon.

3. *Evidences of involvement of the nerve-roots.*—These while variable, still are suggestive of organic changes. Sensory disturbanees are eommon and alterations in the reflexes occur in a large proportion. In some cases the symptoms evidently were due to changes inside the spinal canal causing pressure on the eord. In one of the cases previously reported by the writer there was marked atrophy of the muscles of one leg. The seeond case here reported is of special interest in this eonnection.

4. *Radiograms.*—These have shown definite evidenee of bony ehanges in a sufficiently large number of eases to support strongly the view that organic ehanges are the rule in typhoid spine. It must be remembered that many cases of spondylitis do not show any definite bony ehanges. Brief mention of some of the findings may be made. In the two previously reported by the writer there were definite deposits of new bone in the lower spine. In Silver's ease there was a slight curving of the spine to the left at the juncture of the first and second lumbar vertebræ in the first plate, which had disappeared when a second plate was taken. On the left side of the spine no line of separation between the bodies of the first and second vertebræ could be made out, the bone was denser than normal and there was a shadow between the transverse processes which represented a deposit of new bone. In Myers' case the skiagram showed "a synostosis between the seeond and third lumbar vertebræ with loss of height from disappearance of the intervertebral space." Halpenny[4] in 1909 analysed 72 cases from the literature among which there were ten cases with radiographie examination, in two of whieh no ehanges were found. Some additional cases have been reported in which definite ehanges were found. Carling and King[5] report a case in which the "spines of the eleventh and twelfth dorsal and first lumbar vertebræ were prominent." There was also a deviation of the eolumn to the right. The X-ray plate "showed a very dense shadow over the bodies of the ninth, tenth and eleventh dorsal vertebræ, extending laterally beyond their limits and expanding from above downwards to a point an inch outside the artieular processes on the right side and rather less on the left. The right edge was reetilinear and well defined; the left edge was irregular and not so well defined below." Three weeks later "the main mass of the shadow was less dense, whilst indications of a localisation to the eosto-vertebral articulations could be made out." Wilson[6] reported a case in whieh there was thinning of the intervertebral discs with signs of necrosis in the vertebræ and many osteophytes around them. In connection with these reports it is interesting to note that relatively very few cases of typhoid spine have been reported from Great Britain. Another ease is reported by Godder,[7] in which the "X-ray of the spine shows a diseased condition of the vertebræ at the level of the last dorsal and first lumbar." There is no other note as to the bony changes. In Swett's[8] case there was slight lumbar kyphosis and scoliosis. The X-ray plate "showed a disappearance of the dise between the fourth and fifth lumbar vertebræ, with evidence of new bone formation and the scoliosis beginning at this point." In a reccnt artiele Frick[9] reports three eases without mentioning an X-ray examination. He discusses the whole question at length and gives an excellent bibliography. One of his cases showed the curious rhythmical contractions of the abdominal museles which were noted in one of our earlier cases. In Friek's patient the eontractions were synehronous with the pulse. Potter[10] has reported a case in which the X-ray plate showed "a very dcfinite lesion in the intervertebral disc between the tenth and elcventh dorsal vertebræ. The spaeing between these vertebræ is reduced to about one-half the size it is betwcen the others." There was an increase in the density of the lower part of the tenth and upper part of the eleventh dorsal vertebræ.

5. *Suppuration.*—The occurrence of suppuration is worthy of mention. It has been pointed out that if the condition is due to the loeal action of typhoid bacilli, suppuration might be commonly expected, as typhoid bone lesions in general show a marked tendency to pus formation. Yet one of the prominent features of typhoid spine is the absence of suppuration. In the report of the previous cases the writer suggested that it was exceedingly probable that instances of suppuration would be reported sometime and in this connection a case reported by Myers is of interest. A diagnosis of typhoid spine had been

[4] Typhoid Spine; with the report of a case. Surg., Gynec. and Obst., 1909, IX, 649.

[5] Lancet, 1910, I, 1136.
[6] Lancet, 1909, II, 1279.
[7] Bost. M. and S. J., 1910, CLXII, 711.
[8] Yale Med. J., 1909, XVI, 119.
[9] Interstate Med. J., 1910, XVII, 815.
[10] Med. Rec., 1910, LXXVIII, 1092.

made and a plaster jacket applied. After it had been on for four weeks some odor was noticed and on removing the cast a large granulating wound was found over and to the right of the eleventh and twelfth dorsal spines. The skiagram showed a synostosis of the eleventh and twelfth dorsal vertebræ. Some question arose as to whether the abscess had originated in the bones or was due to pressure of the jacket and cultures did not decide the matter. While this case is suggestive it can hardly be accepted as definitely proved to be an instance of suppuration associated with typhoid spondylitis. An instance reported by Guyot[11] is also not positive although very suggestive. This was in a child who after an attack of what was regarded as typhoid spine, had pain in the lumbo-sacral region. On incision on both sides of the spinous processes, a large amount of pus was found but no proof obtained of any bone lesion. Two days later a focus of osteomyelitis in the left fibula was opened and a few days later one in the right thumb. The patient recovered without any deviation of the spine. However, this cannot be regarded as a definite proved case.

Certain cases in which abscess formation occurred over the lower spine may suggest a possible source in the bone but it is necessary to remember that deep bedsores may extend down to the bone and suggest an origin from it. In fact the necrosis sometimes involves the deeper tissues earlier than the skin. In the absence of positive proof it is not wise to consider these as examples of suppuration due primarily to processes originating in the bones.

Treatment.—As regards prevention it is important to remember the influence of trauma and we should warn the patients convalescent from typhoid fever to exercise care in engaging in any occupation which might throw strain on the spine. When the condition is established it is well to carry out active treatment at once as by doing this we can probably limit the extension of the process in some cases and certainly save the patient suffering. One form of treatment seems well worth a trial, the use of vaccines as in the prevention of typhoid fever. It is to be hoped that this will be tried in the future. The dosage should be the same as that employed in the anti-typhoid vaccination. In treating the established condition two points have especially to be kept in mind, the relief of pain and the protection of the spine, which, as Myers points out, is often structurally weak. The pain is usually lessened by immobilization of the spine as any movement causes great suffering. To secure this some form of fixation is required. Myers favors the use of a brace, pointing out that in the application of a support it is important not to fatigue the patient or injure the spine. He also draws attention to the importance of avoiding anything which will compress the chest. If a jacket is applied this should be done with the patient in a recumbent position and not by the suspension method. Silver mentions the use of the plaster bed and also a gas-pipe frame. It seems important to carry out whatever is adopted as early as possible after the onset of the condition. By this we may shorten the duration of symptoms and perhaps limit the amount of spinal involvement. In the first case reported here the plaster jacket was exceedingly satisfactory and gave the patient great relief. In the first of the cases previously reported by the writer, the jacket failed to give any relief and increased the pain. In such cases or before some appliance can be applied the use of counter-irritation, especially the Paquelin cautery, may give relief. Large doses of sedatives often seem to be without effect on the pain and the quantity of morphia which can be given without any appreciable relief to the patient is remarkable. The fever, which is often present, sometimes diminishes as soon as fixation is carried out, if it be due to the spondylitis. In cases in which it is due to a relapse or a second attack of typhoid fever, one must be guided by the indications. It may be very difficult to carry out any systematic method of hydrotherapy and in such cases expectant treatment is the only resort.

Conclusions.—It may be regarded as established that "typhoid spine" is a spondylitis or perispondylitis with definite local changes which may lead to the formation of new bone and so result in more or less fixation of the spine. Judging from spondylitis generally, this permanent change is less likely to occur if the proper treatment is instituted early. Many cases of spondylitis clear without permanent changes.

[11] Gaz. hebd. d. sc. méd. de Bordeaux. 1906, XXVII, 9.

ERYTHEMA MULTIFORME IRIS DURING THE COURSE OF TYPHOID FEVER.

By H. P. Parker, M. D.,
Professor of Medicine in Howard University, Washington, D. C.

AND

H. H. Hazen, M. D.,
Clinical Professor of Dermatology in Howard University, Washington, D. C.

Before the time of Willan, the various forms of erythema, the acute exanthemata, and inflammations of the skin were grouped together, as was exemplified by the writings of Plenck (1) in 1783. In 1808 Robert Willan (2) separated the erythema multiforme group from the acute exanthemata on the one hand, and from the inflammations due to external irritants on the other. It is interesting to note that in the same volume under the heading of purpura he described what was probably a case of erythema multiforme associated with vomiting, abdominal pain, arthritic pains, and an anasarcous swelling.

In 1835 Rayer (3) cited several cases of Bonnet's to show

that the various forms of erythema might coexist, and in 1854 Hebra (4) showed that the several types of erythema multiforme were forms of one and the same malady. In 1876 Lewin (5) stated that some cases had a fatal termination, and ran the course of an acute infection, though he considered the cutaneous symptoms to be reflex in origin and frequently due to urethral irritation.

In 1895 Osler (6) first published a series of cases in which urticaria, angioneurotic œdema, erythema multiforme and purpura occurred successively or together in the same individual, and in association with a large array of visceral manifestations. Osler supplemented this article by two others, and many other writers, notably Mackenzie (7), Chenoweth (8), Neisser (9), Bulkley (10), Galloway (11) and Sachs (12) have extended this work until we know that the skin lesions of the erythema multiforme symptom complex include urticaria, angioneurotic œdema, purpura, erythema multiforme and nodosum, and if we are to believe Galloway and MacLeod (13) certain cases of lupus erythematosus as well. In the minds of the writers it is questionable whether certain other diseases, notably erythema scarlatinoides and dermatitis herpetiformis should not be included.

Visceral Symptoms.—Any one of the following visceral symptoms may occur; sometimes there are no manifest skin lesions.

Acute tonsillitis, otitis media, laryngitis, phlyctenular conjunctivitis.

Ulceration of the lips and tongue.

Temporary delirium, aphasia, hemiplegia, meningitis.

Gastro-intestinal crises with colic, vomiting, and diarrhœa.

Appendicitis, degeneration of the liver, jaundice.

Enlargement of the liver and spleen.

Bronchitis, pneumonia, pleurisy with effusion.

Endocarditis and pericarditis, anemia.

Hemorrhages from the nose, intestines, stomach, lungs, and kidneys.

Arthritis and infiltration of the synovial sheaths and periarticular structures.

Nephritis and ulceration of the cervix uteri.

Fever, usually irregular and of short duration, but often high.

Etiology.—As regards etiology there have been many theories. In 1835 Gibert (14) wrote that some cases of erythema were symptomatic due to derangements of the internal viscera. In 1850 Bulkley (15) stated that it was especially associated with digestive disturbances and gout. In 1864 Köbner (16) said that it was an angioneurosis due to vasomotor disturbances. In 1876 Lewin mentioned reflex causes, frequently urethral. Chaisse (17), Legendre (18), and Galloway (19) thought that it was due to autointoxication. Finger (20) thought that the local effect of bacteria upon the tissues caused some cases. Many writers, as Singer (21) and Howard (22) found bacteria in the blood, but in the majority of cases the technique of the blood-culture was not above criticism, and Koch's postulates were never fulfilled. As Corlett's (23) case well illustrates some at least were undoubtedly due to streptococcus infections.

Erythema multiforme is also known to occur with such definite infections as typhoid fever, diphtheria, syphilis, gonorrhœa, tuberculosis, cholera, pneumonia, leprosy, malaria, trypanosomiasis, and with suppurative processes in any portion of the body, and may also occur with nephritis and diabetes. Various drugs and antitoxins, and some articles of food also give erythematous, papular, and bullous eruptions that have the same clinical picture as the erythema multiforme group.

Erythema multiforme is frequently spoken of as occurring in typhoid, but we have been able to find only two instances where the eruption occurred during the course of the fever, the cases of Lauffer (24) and Goldstein (25), while Peter's (26) case developed the lesions during his convalescence. Many writers, of whom DaCosta (27), and Hutinel and de Gimard (28) may be taken as fair samples, speak of measley and of scarlatinoid eruptions. Schamberg's (29) article gives an excellent summary of these conditions. In a study of 1500 cases of typhoid at the Johns Hopkins Hospital McCrae (30) notes erythema as occurring 15 times, urticaria twice, purpura 38 times and a pemphigoid eruption once. Thus it will be seen that true cases of erythema multiforme in the course of typhoid are very few.

J. B., a school boy, 14 years of age, a mulatto, was admitted to Freedmen's Hospital on November 5, 1909, complaining of a burning feeling in his eyes, severe headache, great weakness, bleeding from his nose, and a slight cough.

His family history was unimportant, his father, mother and two brothers having died of unknown causes, and his remaining brothers and sisters being in good health.

The patient had suffered from measles, mumps, malaria, and rheumatism, but from no other complaints, though he had had some vague indigestion, and some abdominal pain at night. He was accustomed to drink coffee and a little beer and whiskey, but otherwise his habits were good.

The present illness began two days before admission with a severe headache, which disappeared shortly to be replaced by a burning sensation about his eyes. He was so weak that he had to take to his bed at once. On the following day he had a severe chill, and in the evening nose-bleed. There was some slight cough.

On admission to the hospital the following notes were made:

"The patient is a well-built, well-nourished boy; the facial expression is dull and heavy; the pupils are equal and react to light and accommodation. The tongue is covered with a heavy fur; the pulse is 108 to the minute, regular in force and rythm, of good volume and tension. The chest is well formed and symmetrical; the breathing costo-abdominal in type, 28 to the minute. On percussion and auscultation both lungs are clear throughout. The heart is not enlarged to either the right or the left. The heart sounds are clear and forcible. The abdomen is not distended, it is everywhere soft and tympanitic, the liver is not enlarged, but the edge of the spleen is felt two fingers' breadth below the costal margin. The knee jerks are present."

On admission the temperature was 103° F., and during the illness ran between 100.8° and 103.8° F., the pulse from 80 to 115, and the respirations from 25 to 30. Typhoid was suspected because of the history and initial symptoms, the continued high fever, and the facies. The patient was given an initial purge, and was put on six ounces of milk every four hours, alternating with albumin every four hours. An ice cap was put to the head

and he was sponged every three hours when the temperature rose to 102.5° F., or higher. An enema was given every second day. Six ounces of water were given every two hours. Typhoid isolation was carried out.

Two days after admission the following note was made: "The patient shows over the back of his right hand and extensor surfaces of forearms a number of roughly circular, bluish patches about ½ cm. in diameter. Careful examination shows no rash on any part of the body with the exception of a few small rose-colored patches on abdomen and lower chest that disappear on pressure." Later in the day the following special note on the skin condition was made: "On the hands and forearms, both surfaces, extending half way to the elbow, the fingers, the dorsal surfaces of the feet and the shins there are two varieties of lesions, one of which is macular, ill-defined and varying in size from ½ to 3 cm. in diameter. The other lesion is distinctly annular, from ½ to 2 cm. in diameter, the center is red and the periphery is whitish. The edge is very well defined. On the extensor surfaces of both forearms there are scattered areas or spots that are free from pigment but having a hyperpigmented areola. The proximal finger joints seem slightly swollen, and are bright red in color, the general appearance being similar to the erythematous areas on the arms and legs." It was later found that the patient had suffered every spring for the last four years from an eruption that he described as being similar to the present one save that the lesions became vesicular and burst, leaving these white scars.

The urine had a specific gravity of 1026, and showed a trace of albumin but no casts nor red blood cells. The leucocytes numbered 4400, and a differential count of 500 cells gave:

Polymorphonuclears	66.6%
Eosinophiles	0.4%
Large mononuclears	1.0%
Small mononuclears	29.6%
Transitionals	2.4%

No mastcells or myelocytes.

The Gruber-Widal reaction, 1 to 50 for one hour, was negative. The blood pressure was 110.

On the 9th, two days after the last note, the carpo-phalangeal joints of both hands were red and swollen, and there were a few reddish macules on the proximal phalanges: the annular lesions still persisted on the forearms and backs of the hands and on the feet.

On the 19th there remained only a few annular lesions on both hands and feet. The temperature had now been normal for five days. He left the hospital on the 30th, with the same annular lesions still persisting. Blood cultures and cultures taken from the annular lesions were alike sterile. A Widal reaction, tried just before he left, was noted as suggestive.

Owing to the short duration of the fever, the absence of the Widal reaction, and the marked cutaneous symptoms it was questionable whether the patient was suffering from typhoid fever complicated by erythema multiforme, or from one of the severe forms of erythema with enlargement of the spleen, joint symptoms and continued high fever. In favor of typhoid were the continued high fever, the mental dulness, the coated tongue, and the low leucocyte count. Against typhoid spoke the abrupt onset, and the short duration of the fever, the absence of the Widal reaction and the negative blood culture, although the latter was taken rather late. The other symptoms and physical signs, including the differential count, could have occurred with either disease. A definite diagnosis was not made.

On December 6, one week after his discharge, the patient was again admitted to the hospital. His temperature was 103.6° F., pulse 110, and respiration 30. On the 7th the following note was made: "The patient looks dull and heavy, he complains of headache and pain in his eyes, there is slight discharge from the nose; the patient is not disposed to look at the light. The upper lip is somewhat swollen. The tongue is furred and there is injection of the throat. The chest is negative with the exception of numerous sonorous râles heard during inspiration; these clear up quickly after coughing and are probably transmitted from the larger tubes. The heart sounds are clear. The spleen is easily palpable. There is a marked redness of the palms of the hands and of the heels. A few small rose-colored papules are visible over the various portions of the body. Wherever the patient makes pressure with any part of the body there is a marked erythema. The patient is coughing, and spitting up grayish, frothy, mucopurulent material."

The blood coagulation time, taken by Wright's tubes, was six minutes.

On the 8th the temperature was 104.8° F., pulse 110, and respiration 33. The Widal reaction at one to fifty for one hour was suggestive. A blood culture was taken and an organism found whose cultural characteristics agreed with those of the typhoid bacillus, and which was definitely agglutinated by the serum from a known case of typhoid fever. This made the diagnosis of typhoid fever certain.

On the 10th the leucocyte count was 5700, the red blood cells 4,104,000 and the hæmoglobin 62%. A differential count of 500 cells gave the following results:

Polymorphonuclears	65.2%
Eosinophiles	0.6%
Large mononuclears	.6%
Small mononuclears	25.8%
Transitionals	3.4%
Mastcells	0.0%
Myelocytes	0.4%

The urine showed a large amount of albumin; no casts or red blood cells were noted.

The course of this attack was much more severe, the temperature running as high as 105° F. The treatment was the same as during the first attack with the addition of a mild expectorant for the cough. On the 9th it was noted that the patient was having bloody expectoration. On the 18th he had a rather free epistaxis in the morning and also coughed up a considerable amount of blood, which might of course have come from the nose. On percussion the lungs were clear throughout, but on auscultation there were numerous sibilant râles at the bases, both front and back. Over the chest, abdomen and back there were some pinkish macules about 1 mm. in diameter, and a few other papules that resembled acne lesions. There were no new lesions of erythema multiforme, but the old annular lesions still persisted.

On the 22d of December it was noted that the patient had had a sudden rise of temperature, the temperature previously having fallen almost to normal. Examination showed dulness in the lower right axilla, and impairment of expansion over the same area. Over the right base in front, and over the whole back there were numerous sibilant râles at the end of inspiration. There was no alteration of the breath sounds. These physical signs were similar to those usually found in pneumonia accompanying typhoid.

On the following day the temperature again dropped, and after the 29th there was no fever. Three weeks later the patient was discharged. He still had the annular lesions on the hands and feet, but they were now fading. The same annular lesions persisted from the 7th of November to the 22d of January, 1910, an unusually long time for the annular lesions of erythema multiforme.

It is certain that the patient had typhoid during his second stay in the hospital, and practically certain that he also was

suffering from the same disease during his first admission. During the height of his first attack he had the following symptoms characteristic of the erythemas: annular and macular skin lesions, and swelling and redness of the carpo-phalangeal joints. During the height of his relapse he suffered from œdema of the upper lip (giant urticaria), erythema at points of pressure, and hemoptysis. The fact that these lesions occurred only when the infection was young and active would seem to indicate that the typhoid toxemia was responsible for them.

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ACUTE TUBERCULOUS ENDAORTITIS.*

By Paul G. Woolley, M. D.,

Dean and Professor of Pathology, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

The present consensus of opinion is to the effect that tubercle bacilli cannot, except in the rarest instances, be observed in the circulating blood. Yet we know that they must be present there and often in large numbers. We have built up our ideas of the production of miliary tuberculosis upon the assumption that the organisms that cause the disease are distributed by the blood, to which they gain access in three ways; by rupture of a tuberculous focus in one or another organ into a blood vessel; by the invasion of the walls of blood vessels, especially veins, by the tuberculous process, with the production of a tuberculous lesion in the intima of the vessel from which bacilli are distributed; and by the involvement of the thoracic duct in a tuberculous process, from foci in which tubercle bacilli gain access to the venous blood.

Vascular involvement is frequent, and it is probable that a search in every case of miliary tuberculosis will be rewarded by finding a focus of extension, most frequently in the smaller pulmonary veins, or thoracic duct, less frequently in the renal or pulmonary arteries, aorta, or the vessels of one or another organ of the body.

Invasion *per extensionem* is the rule in small vessels. It is not so common in large ones, nor indeed is vascular involvement of any sort. This invasive process is the one that usually accounts for the production of a generalized tuberculosis. It is the process by which the bacilli gain entrance to the blood stream, whence they are distributed. But there is a second process by which the secondary vascular lesions are produced. It may be assumed to occur generally as the result of thrombosis of, or endothelial phagocytosis in the capillaries of the tissues. As a result of either the vessel wall is involved from the side of the intima. This invasion from the lumen is frequent in small vessels but is infrequent in large ones for obvious reasons. It is least common in the aorta.

A review of the literature on tuberculosis reveals the fact that aortic lesions may be of the invasive or of the metastatic type, and that both are rare. The metastatic lesions may be acute or chronic in character.

In the cases of Dittrich and Kamen the aorta was involved from adherent tuberculous bronchial glands, and this was followed by acute miliary tuberculosis and rupture of the aorta (Kamen). In Buttermilch's case the aortic involvement was secondary to a vertebral tuberculosis.

Schmorl mentions two cases of acute miliary tuberculosis which he conceives as being the result of the perforation of a tuberculous lymph gland or of a pulmonary cavern into the aorta.

Examples of tuberculous aortitis by extension are the cases of Dittrich, Kamen, Schmorl, Hanau and Sigg, and Buttermilch. In the case of Hanau and Sigg an aneurism ruptured

* Read before the Cincinnati Society of Medical Research, October 6, 1910.

FIG. 1.

FIG. 2.

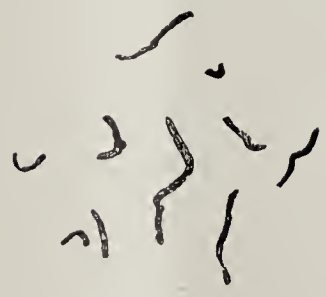

FIG. 3.

into a cavern in the lung. It is entirely probable that the aorta was weakened, its walls infiltrated and an aneurism caused thereby, after which rupture occured, for the edges of the torn wall of the aneurismal sac showed tuberculous vegetations.

The chronic type of tuberculous endaortitis is illustrated by the cases of Forssner, Benda, Aschoff, Longcope, Schmorl, Gaylord, Simnitsky and Luksch.

In this series there has been, with few exceptions, a more or less severe arteritis or arteriosclerosis in association with the tuberculous changes, a coincidence that has lead to the assumption that the specific lesions have been the result of invasion of parietal thrombi by tubercle bacilli. In them the process has apparently shown no tendency to advance along the intima, so that the lesions have increased into the lumen producing either flattened nodules or, more commonly, polypoid growths. In all the cases reported by Benda the lesions were polypoid. In two cases they were situated upon areas of sclerosis, in a third upon an athcromatous ulcer. In Luksch's case the lesions in the aorta, anonyma, and left subclavian were upon an endarteritic basis. In Forssner's case there was no arteriosclerotic change, but it is possible that in this the lesion was primary in the media resulting from a primary involvement of one of the vasa vasorum. The intimal tubercle measured 4 x 1 cm. Stroebes' case was one of a child in which there was a polypoid growth 7 mm. high and 3-4 mm. thick, with no arteriosclerosis. Aschoff's case showed extreme arteriosclerosis and a tuberculous mass the size of a bean near the origin of the Ductus Botalli. The lesion described by Longcope was a polyp 3 cm. long, which was found in the descending aorta of a child suffering from tuberculous hip disease. The report of Simnitsky, to which I have not had access, save through Forssner's paper, concerned itself with a case of chronic pulmonary and intestinal tuberculosis, and no miliary tuberculosis. The aortic lesion was in one of the sinuses of Valsalva.

In all of Schmorl's five cases there was arteriosclerosis, and in all the cases the tuberculous polypi were situated upon atheromatous ulcers.

Accordingly it appears that in this chronic group arteriosclerosis is more frequently present than is natural in tuberculosis, a disease in which the arterial tree is not as a rule severely affected, and it is therefore quite possible that the conception that the aortic lesions are the result of infection of mural thrombi is correct in the majority of cases. Ten of fourteen of the reported cases showed the presence of arteriosclerosis. In two cases I have not been able to find a description of the general aortic condition (Gaylord and Simnitsky) and in two the patients were young individuals (Longcope and Stroebe). In this enumeration Forssner's case is excepted since it is possibly in a class by itself.

The series of acute tuberculous endaortitis include the cases of Marchand, Huber, Schuchardt, Hanot, Hanot and Levi, Simnitsky, Blumer, Flexner and the one to be reported in this paper. In all of these miliary tubercles were present in the intima of the aorta.

The cases of Marchand and Huber were merely mentioned by Weigert who described them as showing the most exquisite structure, "giant cells, caseated center, etc." Schuchardt reported minute lesions situated near the junction of the thoracic and abdominal aorta. There was very little arteriosclerosis. I have been unable to find the report of the cases of Hanot and Simnitsky. That of Hanot and Levy was one in which a tubercle was found in the superior portion of the thoracic aorta. The tubercle discovered by Flexner was situated about 2.5 cm. below the left subclavian artery, and measured 2.5 x 1 mm. in diameter. The aorta was not sclerotic. Flexner believed that this tubercle was secondary to an infective thrombus in the pulmonary artery.

In all of the cases, of either acute or chronic type, the lesions have been described as containing large numbers of tubercle bacilli, a fact that has an important bearing upon the manner of the production of the general miliary tuberculosis that has been present in all except Simnitsky's first case, for many writers believe that the general lesions are the result of the escape of bacilli from the aortic lesions. It would seem reasonable, however, to limit the production of secondary general disease to the chronic cases, for in the acute ones the aortic lesions seem rather to be a part than the cause of it.

The case that I wish to report falls in the category of acute tuberculous endaortitides.

Case 152173.—The patient, a man of 59 years, and a laborer, was admitted to the Cincinnati Hospital on November 11, 1909, complaining of "bladder trouble." In August, 1909, he had been admitted to a hospital for cystitis, which was improved by treatment with urotropin and irrigations. He had suffered with "bladder trouble" for some two years previously, that is to say, he had had pain on micturition, a symptom which was not constant, but which occurred in exacerbations, at the onset of each of which he passed some blood. At the time of his last admission he gave no evidence of pulmonary or cardio-vascular disease, except a slight roughening of the breath sounds during expiration. There was no splenic or hepatic enlargement. He suffered with involuntary urination accompanied by pain. The urine was dark red and contained blood clots.

A week after admission he had a convulsion at 9 p. m., accompanied by a rise of temperature to 102° F., and complained of pain radiating from the bladder to the renal region. There was pain and tenderness in left lumbar region. Subsequently the temperature showed an evening rise. Blood examinations showed a leucopenia, the counts varying from 4400 to 7800. A cystoscopic examination showed that there was a severe cystitis present. The capacity of the bladder was but 90 cc. A diagnosis of "cystitis, probably tuberculous, secondary to tuberculosis of kidney," was made. On December 10, complaint was made of abdominal pain, and on December 12 death occurred. The post mortem was made three hours after death.

Briefly stated the result of the autopsy was that a generalized acute miliary tuberculosis involving the lungs, spleen, liver, peribronchial and mesenteric lymph glands, kidneys, adrenals, pancreas and aorta was found. The bladder and kidneys showed both chronic and acute tuberculous changes.

In the thoracic part of the aorta there were a few fatty streaks, and at the beginning of the descending arch there was one calcified plaque. The abdominal aorta showed an almost completely healthy appearance except at a point 10-15 cm. above the bifurcation, at which point were two small raised areas on the intima

that had the appearance of recent vegetations and which measured about a millimeter in diameter. There was no tuberculous focus in the vicinity of the aorta in the neighborhood of these nodules.

Microscopic examination of the vegetation-like nodules in the aorta showed that they were really intimal tubercles, composed of epithelioid and small round cells, a partial endothelial covering, and a central area of caseation. In them were large numbers of acid fast rods of typical and atypical form, but no giant cells. Beneath these tubercles the media and adventitia were apparently normal, except immediately in the base of the tubercles where there was evidence of a minimal degree of degeneration in the adjacent part of the media.

In the lesions I have studied the bacilli were more numerous in the peripheral parts, and several were observed in the immediate vicinity of the lumen of the vessel. It is possible that some had entered the blood stream, but not in sufficient numbers to cause the appearance of the myriad lesions in other organs.

A further observation of some interest relates to the form of the bacilli in the intimal tubercles. In the cases in the literature, I have not been able to find reference to any other then presumably typical rods. In my case, however, many of the rods were far from typical. Quite a large proportion were of irregular form, and while no actually branching ones could be found, some of them showed bizarre figures that suggested branching.

I believe that in this case the generalized miliary tuberculosis, of which the aortic lesions were a part, was the result of distribution of the organism from the older foci in the kidney, and that it did not result from distribution of tubercle bacilli from the aortic tubercles. The case therefore belongs logically with the group of acute hematogenous aortitides.

It is difficult to account for the lodgment of the organism in these acute cases unless one presupposes at least an incipient degeneration of the cells of the intima, and the formation of ever-so little fibrin in which the bacilli may become entangled. It is very possible that in all cases of general infection and toxemia, more damage is done to the endothelial lining of the blood vessels than we can readily appreciate, a possibility which Baldassari has shown to exist by his observations on the endocardium in cases of infection and intoxication. Certainly it seems simpler to look at the process in this way than to suspect that normal endothelial cells in the aorta are fortunate enough to be able to seize single organisms from the rapidly flowing stream of blood that passes them.

Conclusions.

1. The case here reported is the eleventh of acute tuberculous endaortitis.

2. The aortic tubercles were the result not of extension, but of metastasis from chronic lesions in the kidney.

3. The general miliary tuberculosis that co-existed with the chronic tuberculosis, was not the result of dissemination of organisms from the aortic lesions.

4. The bacilli in the aortic lesions showed bizarre forms with a tendency to branching.

ILLUSTRATIONS.

Fig. 1.—Intimal tubercle. Drawn with camera lucida to show the general microscopic appearance.

Fig. 2.—An edge of the intimal tubercle showing the finer structure of the nodule.

Fig. 3.—Examples of acid fast bacilli showing bizarre shapes.

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REPORT OF A CASE OF EXTENSIVE TIERSCH SKIN GRAFT.

By W. D. Gatch, M. D.,
Assistant Resident Surgeon, Johns Hopkins Hospital, Baltimore.
(*From the Clinic of Professor W. S. Halsted.*)

The case herewith reported has two points of chief interest: the large size of the area grafted, and the demonstration by repeated trials, that only homografts would take in this patient.

Clinical History.

J. C., colored, was admitted to the Johns Hopkins Hospital on November 21, 1909, for flame burns of the back and of the left forearm and hand which he had received fourteen hours before admission. The burn of the back was of the second degree, the others of the first. The photographs show the situation and extent of the former lesion. The area of this was 430 square inches. As the total area of the patient's body is about 2800 square inches, the burn occupied between a sixth and a seventh of his entire cutaneous area.

The patient recovered from the immediate effects of the injury rapidly and with very little general systemic disturbance. While the sloughs were separating the wounds were dressed with a single layer of dry gauze, which was left in place for periods of a week or more, and then changed after giving the patient a prolonged warm bath. Absorbent dressings, changed as often as necessary, were placed over the gauze. This dressing proved very clean and comfortable. In

PHOTOGRAPH TAKEN DEC. 13, 1910, JUST BEFORE THE APPLICATION OF THE FINAL GRAFT.

PHOTOGRAPH TAKEN AFTER HEALING WAS COMPLETE.

less than two weeks the burned surface was covered with healthy granulations. Now followed a long series of attempts to cover the large raw area with skin. These I shall summarize briefly.

On December 16, 1909, 130 "pinch" grafts of rather large size were cut from the patient's thighs and planted over the lower part of the burn. About 110 of these lived, and, together with the epithelium which spread from them, covered an area of very considerable extent.

On December 23, 1909, at the suggestion of Dr. John Staige Davis, the experiment of grafting amniotic membrane was tried, but the epithelium of this failed to take.

On March 1, 1910, and again on March 18, 1910, large numbers of small whole-thickness grafts, obtained from two cases of lipectomy performed by Dr. Kelly, were applied, but these also were all unsuccessful.

On April 1, 1910, several large Tiersch grafts, cut from the patient's thigh, were spread over the granulations covering the right side of the chest. Most of this graft took, although the condition of the granulations was not so good as when the last two grafts were done.

On April 12, 1910, the granulations over the right scapula and the region immediately below were curetted away, and a large Tiersch graft, obtained from another patient, put over the curetted area. As had been the case with all the other isoplastic grafts, none of this lived.

No further attempts at grafting were then made for over five months. During this time the granulations became very deep and œdematous. In places they formed a gelatinous layer half an inch thick, the deeper parts of which were traversed by wide venous sinuses. About one-third of the total burn had now been covered by grafts. It was obvious that before further grafting could be done the granulations must be got rid of. Therefore the patient was anæsthetized (October 25, 1910) and the granulations curetted away down to the fascia, the bleeding being controlled with dry gauze. The cautery was found to cause as much hemorrhage as the curette. The patient was allowed to recover from this severe operation, and the curetted area to cover with fresh granulations. Following this at three separate operations the entire lesion was successfully covered with Tiersch grafts cut from the back of the thighs, and the left arm. These operations were done on November 9, November 23, and December 13.

With but one exception all the grafts were applied to healthy granulations prepared by simple irrigation with salt solution. The skin from which the grafts were cut was prepared by scrubbing with soap and water which was rinsed off with alcohol, and the latter with sterile salt solution. Silver foil dressings, which were usually left in place for ten days, were used. These were covered by very heavy rolls of absorbent cotton and gauze, all held in place by a crinoline jacket.

At present, two months after the last graft was applied, the new skin is freely movable on the fascia beneath. There is no tendency to keloid formation. The mobility of the back is practically normal. The areas from which the grafts were cut are very darkly pigmented. This was true for a time of the grafts also, but the latter are gradually fading to the light chocolate color of the rest of the skin. The total area grafted, determined by tracing its boundaries on a piece of moist crinoline applied over it, is 212 square inches in extent.

None of the isografts applied to this patient lived, though applied under the same conditions as the homografts, practically all of which did so. Dr. J. S. Davis, who has reviewed the cases of skin grafting at the Johns Hopkins Hospital (The Johns Hopkins Hospital Reports, vol. XV, page 307), found that in 499 cases of homodermic Tiersch grafts there were but 13 failures, or 2 3-5 per cent, while in 42 cases of isodermic Tiersch grafts there were five failures or 12 per cent. It has been demonstrated that isografts of highly specialized tissues take far less readily than homografts.* The same is true, but to a less degree of skin grafts.

I desire to thank Mr. Ives and Mr. Fullerton, of the present fourth year medical class of the Johns Hopkins Medical School, for their careful daily dressings of this case for over three months.

*W. S. Halsted, Journal of Experimental Medicine, 1909, XI, 175.

TWO CASES OF CONGENITAL HÆMOLYTIC JAUNDICE WITH SPLENOMEGALY. OBSERVATIONS ON HÆMOLYTIC JAUNDICE.

By William S. Thayer, M. D.,
Professor of Clinical Medicine, Johns Hopkins University,
and
Roger S. Morris, M. D.,
Associate in Medicine, Johns Hopkins University.

In 1900 Minkowski reported the history of a group of individuals belonging to one family, all of whom showed a remarkable syndrome characterised by chronic acholuric jaundice, splenomegaly and urobilinuria. The appearance of these symptoms could be traced through three generations affecting at least eight members of the family. The general health of these individuals was not essentially impaired and no important changes were observed in the blood.

Bettmann, in the same year, described a similar case in which the jaundice displayed marked variations in intensity, deepening after exercise, food, drink and excitement, especially anger, and also after exposure to cold. An experimental

hæmoglobinuria might be produced in this case by the application of cold.

Pick (1903) and von Kranhals (1904) reported like cases, the latter having observed a family of which nine members in three generations showed a chronic congenital splenomegalic jaundice. In all instances the stools were of normal color. The urine which was of a dark color, was free from albumen, blood and hæmoglobin; it showed constantly the presence of urobilin, but never of bile. The number of red corpuscles was below normal, 2,300,000 and 3,500,000 respectively, in the men, and, on one occasion, as low as 1,000,000 in one of the women. The hæmoglobin ranged between 55% and 65%. The red blood corpuscles were irregular in contour and varied in size from 6 to 10 μ. There were no nucleated reds but well marked polychromatophilia.

Minkowski was fortunate in obtaining a necropsy of one of his patients. No especial changes were found in the liver, and the bile passages were quite clear. A small pigment stone was found in the gall bladder. The spleen was enlarged, and microscopically there were simple hyperplasia and hyperæmia. The kidneys showed a brownish discoloration produced by a granular pigment deposit in the epithelial cells of the convoluted tubules. Not only did this pigment give an intense reaction for iron, but there was a large amount of material united with proteids which gave the reaction only after boiling with ammonium sulphide. From but one kidney about 0.95 grammes of pure iron was obtained. Similar pigmentation did not appear in any other organ.

Minkowski regarded the condition as dependent on an anomaly of the blood pigment transformation, perhaps consequent upon a primary change in the spleen.

The clinical picture was not a new one. Similar observations had been made before by Murchison (1883), Wilson (1890) and Le Gendre (1897), and the syndrome appears to be similar to the Chronic Simple Jaundice with Splenomegaly of Gilbert and the Chronic Infectious Jaundice of Hayem (1898). It was, however, Minkowski's observation and necropsy report that first brought this condition sharply before the medical world. During the seven years following Minkowski's original communication, a considerable number of similar observations found their way into the literature: Chauffard (1901); Barlow and Shaw (1902); Mason (1902); Widal and Ravaut (1902); Arkwright (1903); Lortat-Jacob and Sabaréanu (1904); Caporali (1905); Claus and Kalberlah (1906); Strauss (1906); Benjamin and Sluka (1907).

These cases seem to bear a striking resemblance one to another and suggest a common cause. The absence of evidence of hepatic disease and the existence of extensive siderosis, especially of the kidney, in some respects analogous to that seen in Addisonian anæmia, on which Hunter especially has insisted, point to an increased blood destruction as a primary cause of the disease—an hypothesis adopted by most of these authorities.

In 1907 Chauffard made an interesting contribution to the study of this syndrome by the discovery in a similar case, of a marked fragility of the red blood corpuscles on exposure to hypotonic solutions of sodium chloride according to the method of Vaquez and Ribierre. This observation he was able to confirm in two patients presenting a similar syndrome in the wards of his colleague Widal. Thus, while with the normal red blood corpuscles hæmolysis begins at .42%-.44%, and is complete at .32%, in these three cases the beginning and end of hæmolysis were respectively .62% and .36%, .66% and .34%, and .52% and .18%. The average size of the red blood corpuscles was somewhat diminished.

Widal and Philibert on further study, were unable to demonstrate the presence of any hæmolytic properties in the serum of their own patients, either with regard to their own corpuscles or those of other individuals. This fragility of the red blood corpuscles, so marked toward hypotonic salt solutions, was also evident in respect to other hæmolytic substances. The diminished resistance of the red blood corpuscles has been a constant feature in the considerable number of cases of this malady which have since then been reported.

A few months later Chauffard described another interesting hæmatological feature which he had observed in all cases of this disease which had come under his observation, namely: the presence, on vital staining of a peculiar basophilic granulation of the red blood corpuscles. Chauffard's first studies were made by staining freshly made and fixed smears of blood with Pappenheim's (pyronin and methyl-green) solution. Many of the red blood corpuscles which are of a slightly grayish color and barely visible, having lost their refractiveness with their hæmoglobin, show a fine granulation of a bright red color. These dots, generally arranged about the periphery, are sometimes scattered throughout the cells in the form of a definite granulation. The granular corpuscles are usually somewhat larger than their neighbors; they may be demonstrated well by the method of vital staining of Widal, Abrami and Brulé.

Four to six drops of blood are allowed to fall into a test tube containing 10 drops of a basic coloring matter which is quite isotonic and contains in addition oxalate of potassium to prevent the coagulation of the blood.

Oxalate of potassium, 20%, 2 cc.
Unna's polychrome methylene blue, 100 drops } $\Delta = -0.60$

The fresh corpuscles are allowed to remain for 10 to 20 minutes in contact with the solution, after which the mixture is centrifugalized, the supernatant fluid is removed, and the corpuscles drawn up with a pipette and placed upon slides upon which they are spread as an ordinary drop of blood; the covers are then dried and fixed by heat. Such preparations may be preserved indefinitely.

The distribution of the granules is irregular. Sometimes scattered, they are usually collected in groups of two and three. Sometimes they are arranged in the form of a wreath or crown at the periphery of the corpuscle; they are generally distributed in such a manner as to suggest filaments wound around within the cell and showing frequent varicosities; they are unequal in size and of irregular form. Not infrequently

this granular net-work is gathered together toward the periphery or near the centre of the cell in such a manner as to suggest grossly a nucleus.

Sabrazès has called these corpuscles "granulo-reticulo-filamentous." The apparent reticulum is very adherent to the red blood corpuscle. If a dried and stained specimen be washed with pure water the corpuscles lose their blue color, while the granular filamentous appearance remains. Indeed, in some cases the reticulum may be found outside the corpuscle, lying between other well preserved elements. Widal, Abrami and Brulé have thought that the polychromatophilia which is present to a certain extent in these cases, bears a close relation to the presence of granular corpuscles, but this does not appear to be an absolute rule.

It is exceedingly interesting to see how closely these observers agree in their descriptions of this granulation with the careful studies of Vaughan (1903). Although originally described by Pappenheim,* the first careful studies upon the vital staining of the red blood corpuscles were made by Vaughan, who found that this granulation was present in somewhat under 1% of the red blood corpuscles of normal individuals. In the newborn, where they are most frequent, the highest percentage with but one exception (7%) was 4%. In pernicious anæmia with active regeneration, they were found in great numbers (once as high as 18%). In congenital icterus with splenomegaly the percentage is usually over 10%, and figures as high as 40% have been reported. Chalier, however, in his excellent monograph, is inclined to regard these figures as excessive, asserting that he, himself, has never seen a percentage above 20. This granulation, it is needless to say, is quite distinct from the basophilic granulation of Grawitz and others. The granules are different in shape and arrangement and are not to be stained in the fixed specimen. They are, of course, quite distinct from the remarkable Schüffner's granules which appear with Romanovsky's stain in certain parasitiferous corpuscles in tertian and æstivo-autumnal malaria.

It is probable that this phenomenon is simply an indication of active blood regeneration (Vaughan, Ferrata), but there are apparently few conditions in which the frequency of these granular corpuscles compares with that in congenital jaundice—a fact which seems to give them a real diagnostic value.

These observations have been confirmed by a considerable number of observers, and the picture of this disease, which Chauffard has called hæmolytic jaundice, is sufficiently definite to be regarded as a distinct clinical entity.

The patient often belongs to a family other members of which have suffered from the same condition. Early in life, sometimes immediately after birth, but in other cases later, perhaps not until puberty, a jaundice appears. This jaundice is usually of a moderate degree varying from a pale lemon hue to a well marked golden yellow. It is remarkably variable, increasing often under physical effort or emotional excitement. The stools are of normal color or pleiochromic, especially under those conditions associated with increase in jaundice.

The urine is of rather high color, often of a brownish almost mahogany hue, but free from bile. Urobilin is usually demonstrable. The blood shows an anæmia of moderate degree, generally between 3,000,000 and 4,000,000 red corpuscles, although in one case a blood count of under 2,000,000 is reported. There is usually considerable anisocytosis, but little or no poikilocytosis. The average size of the corpuscles is sometimes rather below the normal, a point upon which Chauffard particularly has insisted. The color index is somewhat reduced. Polychromatophilia is usually well marked. On vital staining the granulation described by Pappenheim, Vaughan, Sabrazès, Chauffard and others is present in a large number of corpuscles. The percentage of granular elements is usually above 10% and may be as high as 20%, or even more. The serum is of a clear, yellowish color, and the test for bilirubin is positive. Urobilin is generally undemonstrable. The leukocytes are usually of normal number or slightly increased. The differential count shows nothing remarkable beyond evidences of increased marrow activity as manifested by a high percentage of eosinophiles and the occasional presence of myelocytes and nucleated red cells—normoblasts.

The serum shows a rather high degree of hypertonicity. Starkiewicz regarded this condition as a mechanism of defense on the part of the organism to protect the fragile red corpuscles. Troisier, however, believes it to be the result of exosmosis of the corpuscular salts as a result of the fragility of the red cells.

The remarkable feature of this interesting condition is that subjective symptoms are usually absent despite the constant anæmia. The patients are generally unconscious of any disability. They appear to adapt themselves so well to their condition that it is only occasionally that a complaint is elicited. There is a complete absence of all the ordinary phenomena of biliary intoxication: there is no bradycardia; no pruritus; no tendency to hæmorrhage; no xanthelasma. The patients are, indeed, as Chauffard has gracefully said, "à peine des malades—plutôt des ictériques que des malades"—barely patients, rather icterics than patients.

There is one exception to this rule. Many of these individuals suffer from attacks of abdominal pain suggestive of biliary colic. These pains, localized in the epigastrium and in the region of the gall bladder, are often accompanied by fever and by an aggravation of the jaundice. In a number of instances they have been so severe as to lead to operation. In many cases it is probable that the attacks are due to the presence of small pigment stones in the gall bladder, such as have been found in four of the six cases of congenital jaundice that have come to necropsy—every instance but one in which the gall bladder was examined.

In the last several years the authors have had the opportunity of observing two striking cases of congenital hæmolytic jaundice which appear to be worthy a note of record.

* This subject is well discussed by Ferrata who, however, in common with every continental author, ignores Vaughan's excellent work.

Case I.—Miss X., 16 years of age, a school girl, consulted one of us (W. S. T.) on the 30th of May, 1906, with a complaint of jaundice. Her father and mother were well and strong. She has one sister, younger than herself, who is perfectly well, and the family history in other respects, is good.

Her mother states that as an infant the patient used to have slight attacks of jaundice for which they were accustomed to give her calomel, but as she grew older the attacks became more frequent until, finally, the jaundice became permanent. The yellow color has varied in intensity from time to time, but the mother is not sure that it has ever been wholly absent. It has been deeper as a rule at the time of menstruation, and worse after exertion and bad colds, or with any indisposition. Six years ago the patient had a febrile attack which was regarded as typhoid fever. In other respects she has been a strong healthy girl, taking part in all the out-of-door games of her companions. She is not conscious of having been short of breath.

Eight months ago she began to have occasional attacks of pain in the right side of the epigastrium, lasting from ten to twenty minutes. Of these attacks she has had several. Three weeks ago she had a paroxysm of sharp, cramp-like pains in the same position, so sharp that at times while at school she had to lie down; there has been no fever with any of these attacks, but in the last three weeks she has had more or less pain, usually every other day. Lately the jaundice has been worse, but it is the pain that has excited the attention of her parents.

In other respects she had felt perfectly well and only recently, since she has grown older, she has been somewhat annoyed by the consciousness of her jaundice.

On examination there was a distinct jaundice although in other respects the color of the patient was that of a healthy girl; the tongue was clean; pulse 19 to the quarter, regular, not remarkable. Examination of heart and lungs negative.

Abdomen, natural; no tenderness on pressure in the region of the gall bladder; palpation, negative, although, on light percussion, there is possibly a very slight suggestion of dulness in the region of the gall bladder. The spleen in readily palpable, descending on deep inspiration at least 4 cm. below the costal margin.

Widal reaction, negative.

Blood:

R. b. c.	3,680,000
W. b. c.	800,500
Hb.	70-71%

Dried and stained specimens showed the red blood corpuscles of about normal size with but slight variation in diameter; the color is good; no marked polychromatophilia. Their contour is fairly regular, but there is some distortion, a few elliptical and dumbell shapes being found. No nucleated reds.

Differential count:

Polymorphonuclear neutrophiles	72.5 %
Small mononuclears	18.0%
Large mononuclears	7.5 %
Transitionals	1.5 %
Eosinophiles	.5 %

The case was regarded as one of chronic, congenital jaundice with splenomegaly of the type described by Minkowsky. There was a question as to the existence of gall stones, but, in the absence of severe symptoms, operation was not advised. Blaud's pills to be continued through long periods of time, were prescribed.

Three years later, having become familiar with the work of Chauffard, Widal and others, the writer requested the parents of the patient to allow him to see her again. She was accordingly seen on the 20th of March, 1909. Jaundice had been present for the greater part of the preceding three years, although the patient had grown and developed normally and was a perfectly healthy looking girl. The mother says that after long periods in the house she becomes more jaundiced and that dancing, violent exercise and bad colds make it worse. It is worse at the catamenial periods, better just afterwards. The author's note on this occasion reads:

"Strong, healthy looking girl; color good; tongue clean. There is a distinct slight jaundice of the skin and conjunctiva. Pulse 22 to the quarter, regular, not remarkable in quality. Heart sounds, clear at the apex and base.

Abdomen: natural in appearance. Spleen, readily felt just below the costal margin, descending on deep breath 3 or 4 cm. below. It seems smaller than when last seen. The liver descends just below the costal margin on deep breathing; flatness above at about the 6th rib, extending to the costal margin. Gall bladder, not felt.

Blood:

R. b. c.	3,200,000
Hb.	75%

Resistance of the red blood cells: 1 cc. of blood was collected in 9 cc. of 1% aqueous sodium fluoride solution, and the corpuscles were subsequently washed three times in 0.85% NaCl solution. A 5% suspension of the red corpuscles in 0.85% salt solution was prepared. The corpuscles were then placed in solutions of NaCl of varying strength and the first trace of hæmolysis (minimal resistance) and complete hæmolysis (maximal resistance) noted. The results showed:

Minimal resistance	0.68% NaCl.
Maximal resistance	0.45% "

After centrifugalizing the blood-sodium fluoride mixture, the supernatant fluid was found to be of a canary yellow color; it was pipetted off and tested for urobilin and bilirubin. Neither pigment could be demonstrated, using the technique described by Conner and Roper.

Urine.—Fresh specimen March 20, 1909. Brownish yellow, clear, acid, sp. gr. 1.014; albumen and sugar absent; bile: foam white; tests with yellow nitric acid negative. Trousseau's test (tincture of iodine) negative. Urobilin: marked green fluorescence on treating the amylic alcohol extract with 1% $ZnCl_2$ in ammoniacal alcohol; also positive on spectroscopic examination.

On the 4th of April, after taking Blaud's pills gr. V, t. i. d. for two weeks, the patient allowed us to make another examination of the blood:

R. b. c.	3,800,000
W. b. c.	5,200
Hb.	84% (Dare.)

Vital staining of fresh blood with Unna's polychrome methylene blue, according to the method of Vaughan, showed 149 red cells with basophilic granulations out of 1228 cells examined, or about 12.1% (normal = 0.5% to 1.8%.—Vaughan).

Differential count of 564 cells with Ehrlich's triacid stain:

Lymphocytes	18.6%
Large mononuclears and transitionals	3.5%
Polymorphonuclears, neutrophilic	73.0%
Polymorphonuclears, eosinophilic	1.2%
Polymorphonuclears, basophilic	0.7%
Myelocyte, neutrophilic	0.17%
Degenerated	2.6%

Wilson's stain (Romanovsky) and the triacid stain were used in studying the red cells. There was moderate anisocytosis, no poikilocytosis. The red cells were of good color and no polychromatophilia, basophilic granules, nuclear particles, Cabot's ring

bodies, or nucleated reds were seen. The blood platelets were rather few in number in the stained specimens.

Resistance of the red blood corpuscles:

Minimal resistance ..... 0.72% NaCl.
Maximal resistance ..... 0.42% "

The blood plasma-sodium fluoride mixture was again of a brilliant canary yellow color. Using the methods recommended by Conner and Roper, bilirubin was demonstrated; tests for urobilin were negative.

Urine.—Fresh specimen, April 8, 1909. Yellowish brown, clear, acid, sp. gr. 1.024; albumen, sugar and bile, absent. Urobilin: marked positive reaction, both chemical and spectroscopic. Microscopical examination showed a few squamous epithelial cells; otherwise negative.

Stool.—Dark brown, small, constipated stool. No blood, pus or mucus. Microscopical examination: a few muscle fibers without striations, many yeast cells. No ova or parasites. Schmidt's test (concentrated corrosive sublimate) positive for urobilin, negative for bilirubin.

Blood.—The average diameter of 500 red corpuscles in dried and stained specimens (Wilson's modification of Romanovsky) was 7.45 μ. The variations were between 5 and 9.4 μ—essentially normal measurements.

In July of the same year the patient was seen in Europe. At that time she seemed perfectly well but showed, as always, a distinct slight jaundice of the skin and conjunctivæ.

The general appearance of the patient was very remarkable. Without observation one would have picked her out as a perfectly healthy girl; her cheeks were red and her expression bright, the general nourishment good and it was a matter of great surprise to find so marked an anæmia. She had never been short of breath and complained of no subjective symptoms of anæmia.

The second case was seen in the wards of Prof. Barker, to whose courtesy we are indebted for the privilege of reporting the case.

Case II. (Med. No. 23623).—F. B., single, age 27, a manicurist, was admitted to the hospital on January 22, 1909, complaining of jaundice. The family and personal history are good. No other member of the family is jaundiced. The patient has had measles at 9, mumps at the same age and whooping-cough at 12. During the last twelve years there have been occasional attacks of major hysteria, usually following mental shock. There has been chronic constipation. The patient has been jaundiced since she was three days old; the jaundice is variable, sometimes very deep and again scarcely noticable. Since the age of 16 she has complained of what she called bilious spells about twice a month. While dressing in the morning she becomes nauseated, vomiting one or two ounces of fluid, at first like water and then almost pure bile. A few minutes after vomiting she feels relieved and is able to go to work.

There is no history of pain in the region of the gall bladder, or of hæmatemesis. The patient has not passed acholic or bloody stools to her knowledge. She has had no abdominal pain. In July cholecystostomy was performed by Dr. John D. Blake. No gall stones were found.

About two months ago the patient began to have a "dead, aching pain" a little below the right scapula; the pain seldom shifted. There has been slight pain occasionally above the left nipple. Her average weight is 138 lbs.; in the last three months she has lost 13 lbs.

Status presens. (Dr. Boggs).—The patient is well nourished. There is a marked icteric tint to the entire skin, the scleræ and the mucous membranes. No xanthoma. The lungs are negative. Heart : Apex is just felt in the 4th interspace 9.5 cm. to the left of the median line. Relative cardiac dulness extends 10.5 cm. to the left in the 5th, 3.5 cm. to the right in the 3rd interspace, and above to the 3d rib. There is a soft systolic blow at the apex, transmitted to the axilla. Pulmonic second sound accentuated. There is a blowing systolic murmur over the conus.

Abdomen: Spleen extends 4 cm. downward and forward beyond the costal margin. Liver not palpable. No hæmorrhages noted.

Jan. 29. (Dr. Thayer). Perfectly healthy looking woman with yellowish type of jaundice. Tongue clean. Abdomen slightly more prominent on left. Spleen readily palpable. Liver not enlarged.

Feb. 5. (Dr. Hanes). Since admission the patient's only complaint, jaundice, has varied very markedly from a light yellow to a deep lemon color. The scleræ are constantly yellow and do not vary as much as the skin. The heart is as noted before,—the systolic blow is very faint and is not transmitted to the axilla. Spleen still enlarged, edge firm and sharp. Patient discharged.

During the patient's stay in the hospital, her blood pressure (systolic) varied between 100 and 118 mm. Hg. The temperature was between 97.6° and 100.2° F. Pulse 60 to 83, respirations 18 to 20.

Blood examinations:

Jan. 23. R. b. c. 3,800,000
W. b. c. 8,900
Hb. 70%

In the fresh blood the red cells appear normal in color and shape. No nucleated reds or parasites.

Jan. 26. Wasserman reaction negative. Coagulation time, 5 min.

Jan. 27. Blood count practically the same as on the 23d.

Jan. 28. (Dr. Hanes). The patient's blood serum is of a golden yellow color, and the HNO_3 test for bile is positive.

Jan. 29. (Dr. Rous). "Resistance of the red blood cells to hypotonic salt solution. Into a series of tubes containing 1 cc. each of dilute salt solution 20 mm. of the patient's whole blood were dropped. The dilutions comprised a series from 0.85% to 0.10% NaCl. As control, the blood of S., who had about the same number of cells per cm., was taken. The corpuscles of S. showed complete hæmolysis at a dilution of 0.30% and those of the patient at 0.40%. (This is an immediate observation). After 24 hours the reading showed a trace of hæmolysis at 0.55% for S., and about the same at 0.75% for the patient."

Differential count of 400 cells showed:

Lymphocytes ..... 47.0 %
Large mononuclears and transitionals... 5.25%
Polymorphonuclear neutrophiles ..... 46.0 %
Polymorphonuclear eosinophiles ..... 0.5 %
Mast cells 0.25%
Unclassified 0.75%
Feb. 3. R. b. c. 3,700,000
W. b. c. 10,500
Hb. 76%
Viscosity 4.1 (in terms of distilled water).

Stool examinations were made on Jan. 27 and 29 and on Feb. 3. Schmidt's test showed only hydrobilirubin. Microscopically nothing of importance was found.

Urine was examined on six different days. Sp. gr. 1.018 to 1.030. There was no albumin or sugar. No bile or bilirubin was demonstrated. Urobilin was tested for apparently only on Feb. 4th, when the report says, "Schlesinger's urobilin test negative. Spectroscopic examination inconclusive." The color of the urine was described as brownish yellow and orange.

It is rather unfortunate that more careful tests for urobilin were not made; it must have been present.

All attempts to communicate with the patient since her discharge from the hospital have failed.

These cases are typical examples of this condition. Although both patients showed a well-marked jaundice, in neither was there the slightest disturbance in the shape of itching; in neither was there bradycardia. The complaint of the second patient bore apparently no relation to her jaundice. The extraordinary manner in which these individuals adapt themselves, as it were, to their anæmia, is strikingly illustrated by both of our patients, especially by the first, whose appearance and history were not of a delicate but rather of a robust, strong girl.

A striking peculiarity in the observations made upon this case is the remarkably high point of concentration of the solutions of sodium chloride at which complete hæmolysis appears, .42% and .45%, a concentration equal to or above that at which, in the normal individual, hæmolysis begins.

Acquired Hæmolytic Jaundice.—This remarkable syndrome, chronic acholuric pleiochromic jaundice without the usual symptoms of biliary intoxication, associated with anæmia, enlarged spleen, and siderosis of the viscera is not, however, always of congenital origin. Soon after Chauffard's first observations, Widal and Abrami, Chauffard and Troisier, Le Gendre and Brulé, von Stejskal, Oettinger, Parkes-Weber and others reported a series of interesting observations in which a similar train of symptoms came on without apparent cause in adult life. The onset of the jaundice in these instances followed various different accidents—an ischio-rectal abcess (Widal and Abrami), hæmorrhage following a miscarriage (Widal and Abrami), severe nervous shock (Chauffard and Troisier), acute gastro-enteritis (Le Gendre and Brulé). In other instances, such as the two cases of von Stejskal, that of Oettinger, and that of Parkes-Weber, the process seems to have appeared without striking initial symptoms. Again, in a considerable group of cases a jaundice of a transient character presenting similar hæmatological phenomena—an anæmia with signs of regenerative activity of the bone marrow, granular corpuscles on vital staining and a marked fragility of the red cells, has been observed in the course of a variety of conditions, cancer of the stomach (Chalier); cirrhosis of the liver (Chalier and Le Play); malaria (Sacquépée, Chalier); repeated hæmorrhages in cancer of the bladder (Widal and Joltrain); streptococcus infection (Sacquépée); uncinariasis (Darré); syphilis (Gaucher and Giroux); pulmonary tuberculosis (Landouzy); jaundice of the new born (Sabrazès and Leuret; Cathala and Daunay).

This acquired hæmolytic jaundice, as it has been called by Widal and Abrami, who described the first cases, does not constitute a definite disease picture to the same extent as does congenital splenomegalic jaundice, but rather an interesting syndrome. Acquired hæmolytic jaundice may be divided, as suggested by Brulé, into apparently *primary* and *secondary* cases. The former arise either without apparent cause or during the course of some acute transient malady, after which they persist with seeming independence. Secondary hæmolytic jaundice is observed in a transient manner associated with acute infections or poisons, or as a terminal phenomenon in the course of some chronic disease.

One essential difference exists between most of the cases of acquired hæmolytic jaundice and the congenital malady, namely: the existence in the former of an anæmia sufficiently grave to occupy a prominent position in the clinical picture. The anæmia may, indeed, be intense and is associated with the usual subjective symptoms. There are often striking variations in the intensity of the jaundice and the grade of anæmia. Sudden paroxysms of fever associated with painful swelling of the spleen and extremely rapid fall in the number of red corpuscles have been described.

A patient of Widal and Abrami's showed, on the 19th of May, 2,600,000 red blood corpuscles; ten days later, while in apparently good condition, there appeared severe headache, dyspnœa, marked exacerbation of the jaundice, and in a day or two the blood count showed but 850,000 red elements. In one of von Stejskal's cases the blood count rose in eighty days from 640,000 to 4,000,000.

The blood picture is often very similar to that in pernicious anæmia; marked oligocythæmia; a high color index; anisocytosis; poikilocytosis; often an increase in the average corpuscular diameter. There are almost always marked evidences of marrow activity in the shape of nucleated red blood corpuscles, among which megaloblasts are often found. Contrary to what one sees in pernicious anæmia, the leukocytes are usually somewhat increased, and, occasionally, there is a well-marked leucocytosis, which, on differential count, shows a considerable proportion of myelocytes and a large percentage of eosinophiles. Granular corpuscles are present on vital staining, as in the congenital form of the disease; sometimes, however, these are not so numerous.

There are two striking points of difference in the hæmatological picture between acquired and congenital hæmolytic jaundice. The corpuscular fragility, so evident in the former condition, is often very slight in the acquired disease when the test is made with unwashed corpuscles.

Widal and Abrami showed early that in acquired hæmolytic jaundice the corpuscular fragility may, indeed, be almost inappreciable if the test be made with the whole blood. With deplasmatized corpuscles, however, the resistance is distinctly, sometimes very markedly, diminished. These authors showed that this increased fragility of the deplasmatized red corpuscles is common to both congenital and acquired varieties of the disease with the essential difference that while in congenital hæmolytic jaundice the fragility is usually demonstrable with the whole blood, in the acquired condition the resistance of the whole blood may be normal, while that of the deplasmatized corpuscles may show a very marked reduction. The deplasmatized red blood corpuscles of acquired hæmolytic jaundice show also a distinct diminution in resistance toward other hæmolytic substances, such as anti-human sera of all sorts and leech extract.

In normal blood the resistance of the deplasmatized corpuscles does not differ essentially from that of the whole blood.

While it is difficult to avoid the conclusion that this increased corpuscular fragility has a definite association with the hæmolysis which occurs in these cases, yet it should be

remembered that no direct parallelism can be drawn between the degree of fragility and the extent of the anæmia. The conditions existing in congenital and acquired hæmolytic jaundice form an interesting paradox, as has been pointed out by Brulé; on the one hand a marked corpuscular fragility associated with a moderate anæmia, on the other a moderate fragility and an intense anæmia. "It is impossible to draw a direct conclusion as to the fragility of the red blood corpuscles in the organism from their fragility in vitro."

This diminution in the resistance of the deplasmatized corpuscles may be restored if they be brought into contact again with their plasma. Although there is a slight difference between the resistance of the corpuscles according to the manner in which they are separated from their plasma (Iscovesco, Salignat), yet these differences are so slight that they need not be considered; in fact the quantity of serum necessary to restore the resistance of separated corpuscles is so large that, practically, it is unnecessary to wash the corpuscles deplasmatized in an oxalate solution. The anti-hæmolytic power of the serum is not restricted to that of the patient himself. It is present in other and heterologous sera. Heating to 56° C. for a considerable period of time does not remove the power. There would then appear to be no evidence of the existence of a specific anti-hæmolytic substance. Widal, Abrami and Brulé believe that the anti-hæmolytic power is dependent on some special physical property or properties of the serum.

The blood of some individuals with acquired hæmolytic jaundice possesses one characteristic which, for the moment, appears to be rather special, and is not observed in the congenital forms, namely, an auto-agglutinative power of the serum. The test is a relatively simple one; it is thus described by Brulé.

"One lets fall into a watch glass 10 drops of the patient's serum and then a drop of red blood corpuscles isolated by centrifugation: the mixture is shaken up and then allowed to rest. Soon the corpuscles are seen to gather at the bottom, sometimes appearing to form little masses. But if there is no auto-agglutination, we need but to shake the glass slightly to restore the mixture to its previous homogeneity and to disperse the corpuscles in the serum. If the auto-agglutination be positive, one sees after a period varying according to the intensity of the phenomenon, from one to twenty minutes, a collection of the corpuscles into little granules easily perceptible by the naked eye, which give the emulsion an aspect comparable to brick dust; violent and prolonged shaking cannot dissociate these corpuscles. Little by little the agglutination increases, the corpuscles gather at the bottom of the watch glass where they form an homogeneous pellicle, the supernatant serum becomes limpid, and shaking no longer dissociates the hæmatic pellicle. If at the beginning of the phenomenon one examines a drop of the serum microscopically it may be seen that the corpuscles, instead of disposing themselves in rouleaux as normally, gather in little islands, between which there float a few isolated corpuscles."

This phenomenon has been found in a number of instances of acquired hæmolytic jaundice. In others, such as the cases of Widal and Joltrain, and that of Parkes-Weber, auto-agglutination has been absent. The phenomenon is interesting and may be of considerable diagnostic value. It is not present in congenital hæmolytic jaundice, although the patient of Bénech and Sabrazès, whose jaundice is believed by the authors to have been acquired from a wet nurse, might be regarded as belonging to this class. It has, however, been observed in one instance of hepatogenous jaundice by Brulé. It should be said that it has not as yet been studied sufficiently to justify far-reaching conclusions as to its diagnostic value or significance.

Attacks of pain in the region of the gall bladder associated with fever and exacerbation of the jaundice are very common. Indeed, the first three reported cases (Widal and Abrami; Chauffard and Troisier) were all operated upon for suspected gall stones. In one of these cases a little bile sand was found; in the other instances the gall bladder was quite clear.

Acquired hæmolytic jaundice presents itself in a variety of forms. The most important are:

1. Those cases simulating cholelithiasis.
2. Those simulating pernicious anæmia with jaundice.
3. Those simulating a chronic infectious cholangitis, chronic, infectious, splenomegalic jaundice (Hayem).
4. It has also been observed in some of those conditions in which the most striking symptoms, anæmia and splenomegaly, leave one in doubt as to whether the case should be classed clinically as Banti's disease or a cirrhosis of Hanot's type. Recent studies by Chauffard and Troisier, as well as by Armand-Delille and Feuillé, suggest strongly the possible relationship between some so-called splenic anæmias and hæmolytic jaundice. Attention has also been called to this point by Parkes-Weber.

In other instances the condition may manifest itself under the symptoms of an *icterus gravis* (Roque and Chalier).

The syndrome is, however, sufficiently definite and easily to be recognized if carefully studied, by the absence of bile in the urine, its presence in the blood serum, the urobilinuria, the presence of a large percentage of granular corpuscles on vital staining, by the fragility of the red corpuscles, especially manifest with the deplasmatized elements, and by the commonly present auto-agglutinative power of the serum.

It is important to remember that in Addisonian anæmia and in cholelithiasis the corpuscular resistance is at least normal; indeed, as a rule, it appears to be increased. In one of my cases of pernicious anæmia hæmolysis began at only .325%, and was complete at .275%, a greatly increased resistance.

In obstructive jaundice Vaquez and Ribierre have also shown that the resistance of the red corpuscles is as a rule distinctly increased, an observation which we have been able to confirm.

Pathological Anatomy.—Several individuals presenting the syndrome of hæmolytic jaundice have come to necropsy (Vaquez, Giroux and Aubertin; Oettinger; Gandy and Brulé; Widal and Joltrain; Roque and Chalier; Micheli; Möller; Wilson; Tileston and Griffin). The cases of Vaquez, Giroux and Aubertin, Gandy and Brulé, Wilson, and Tileston and Griffin, were apparently of congenital origin; the others, probably acquired. In all cases, however, the essential features appear to have been general evidences of an hæmolytic process as

manifested by a siderosis of liver, spleen and kidneys. The autopsy in the case of Vaquez and Giroux is of especial interest as it occurred in a congenital case in which death followed splenectomy, so that complications with other terminal processes were ruled out. The lesions which have been confirmed in the later cases, were as follows:

A marked congestion of the spleen especially confined to the pulp, the engorgement of which was in rather striking contrast to the relative emptiness of the sinuses. There were few macrophages in the splenic pulp, more in the sinuses. The endothelial cells were stuffed with iron containing pigment.

The liver showed no evidence of biliary obstruction, no angio-cholitis. Many of the liver cells, especially in the centro-lobular zones, were, however, stuffed with large granules of ochre pigment.

There was moderate siderosis of the cells of the convoluted tubules of the kidney, and marked hyperplasia of the marrow.

These observations have been confirmed, in great part, in all cases which have come to necropsy, affording thus abundant evidence of the hæmolytic character of the process. The siderosis of the kidney, which is usually present, has, however, been very moderate in some instances, and was apparently absent in Gandy and Brulé's case of congenital hæmolytic jaundice, where death occurred in the course of a pneumonia as well as in Micheli's instance of the acquired form of the disease. In no instance was there evidence of biliary obstruction.

Pathogenesis.—The pathogenesis of this remarkable syndrome is by no means clear. The evidence of a chronic hæmolytic process is not so very different, indeed, from that which one sees in various other conditions, such especially as Addisonian or bothriocephalus anæmia, conditions in which chronic jaundice is not uncommon. The clinical picture in some of the acquired forms of the disease with crises of aggravation of the malady, may almost resemble paroxysmal hæmoglobinuria. Here, as Donath and Landsteiner have shown, there is in the serum a true auto-hæmolysin. But in paroxysmal hæmoglobinuria there is no evidence of a diminished resistance of the red blood corpuscles.* In Addisonian anæmia, as has already been said, the resistance of the red blood corpuscles is usually increased.

On the other hand there is no evidence of a specific hæmolysin in these instances of jaundice associated with corpuscular fragility, so that one has been tempted to separate an hæmolysinic jaundice, such as the jaundice with pernicious anæmia or that seen with paroxysmal hæmoglobinuria, from the jaundice associated with corpuscular fragility, to which the name *hæmolytic* has come to be applied—a deplorable complication of terms.

This is, however, not to say that the primary causal element in some of the instances of so-called acquired hæmolytic jaundice may not be the presence of toxic hæmolytic substances in the organism. Indeed, there is some reason to believe that this may be the case. Troisier, for instance, in his recent thesis advances various arguments in support of the hypothesis that the fragility of the red corpuscles in these cases of hæmolytic jaundice is dependent upon the fact that they have already become sensitized by union with an hæmolytic amboceptor.

However this may be, we are in the presence of a remarkable clinical syndrome—acholuric, pleiochromic, jaundice, anæmia, corpuscular fragility, granulation of the red corpuscles on vital staining, post-mortem evidences of blood destruction in the form of siderosis of the liver, spleen and kidneys, absence of evidence of the presence of hæmolytic substances in the serum.

Several questions naturally suggest themselves.

1. Where does the hæmolysis take place?

2. Where does the bilirubin circulating in the blood find its origin?

3. What is the primary cause of this condition?

1. As to the manner and seat of the hæmolysis there have been varying opinions. Some (Minkowski, Chauffard, Vaquez) fancy that, gathered in the pulp of the spleen which, as has been seen, is always markedly engorged, the abnormally fragile corpuscles are there destroyed. Others (Widal and his pupils) are inclined to believe that the destruction occurs in the general circulation, the débris accumulating as it always does in the spleen, and accounting thus for the symptoms and manifestations on the part of that organ. One observation, as pointed out by Castaigne, is strongly in favor of the circulatory origin of the hæmolysis, namely, the siderosis of the kidneys, which is often demonstrable. Otherwise no important evidence can be adduced in support of one or the other of these views which, in the end, are essentially the same, excepting in so far as they bear upon the second question.

2. *The Cause of the Jaundice.*—Most observers have believed the jaundice to be immediately hepatic in origin due to the over-production of bile by a liver overstocked, so to speak, with the products of blood destruction. The old idea that this was, in a sense, after all, an obstructive jaundice owing to the inspissation of the bile and the engorgement of the intra-hepatic bile passages, or to a diffuse intrahepatic cholangitis, must, however, be abandoned as a result of the clinical and pathological observations of some of these cases. If the hepatic origin of the jaundice be accepted, we must fall back upon the assumption of Minkowski, that the overworked hepatic cell gives off a part of the excess of bile which it produces into the capillaries, as well as into the bile passages.

Widal and his pupils, however, advance another hypothesis, which is in many ways inviting. Pointing out the rapidity with which jaundice follows experimental blood destruction in animals, they call attention to the lack of evidence of any inspissation of the bile, referring especially to one of their patients on whom a cholecystostomy was performed for suspected stone. The gall bladder and ducts were empty, and the bile which was discharged from the fistula in large quanti-

* It is true that Meyer and Emmerich believe that they have been able to demonstrate a diminished resistance of the red corpuscles in paroxysmal hæmoglobinuria against changes of temperature, dilute acids and saponin. Meyer and Emmerich: Ueber paroxysmale Hæmoglobinurie. Deutsches Arch. f. klin. Med., Leipsig, 1909, XCVI, 287-327.

ties, was of normal character, and strikingly fluid. On the other hand they observe that Langhans and Quincke have demonstrated bilirubin in the seat of old hæmorrhagic foci, that Sabrazès and Muratet have observed the presence of urobilin in cerebro-spinal fluid after cerebral hæmorrhage, and that Froin has shown that hæmoglobin may be changed into biliary pigment in hæmorrhagic exudates in the meninges and in the pleura, observations which have been confirmed by Guillain and Troisier, Widal and Joltrain and others. The urobilin which various observers have demonstrated in the serum they believe to be due to a direct transformation from hæmoglobin through bilirubin such as has been shown to occur in hæmorrhagic exudates (Troisier: Thèse). They point to the fact that in cases presenting the syndrome of which we have been speaking, despite the long-continued jaundice, there is no evidence of the ordinary symptoms of biliary retention, symptoms which they believe to be due to the action of biliary salts, namely, pruritus, bradycardia and emaciation. Bile acids have never been found in blood or urine. Nor do the red corpuscles show the increased size and heightened resistance to hypotonic salt solutions which Rist and Ribadeau-Dumas believe to indicate an acquired tolerance for intoxication by taurocholate of sodium. Everything, they think, points to the existence of a purely pigmentary cholæmia which, theoretically, might easily arise in the blood itself. This is a conceivable and seductive hypothesis. The objections based upon the absence of hæmoglobin in the circulation, which have been raised against this idea are answered by Widal by the assumption of a destruction of the corpuscles so gradual that the quantity of hæmoglobin is too small to be recognizable. It cannot be said, however, that the symptoms of ordinary biliary intoxication are never present, rare though they be, for itching has been observed in one or two instances. On the other hand the argument that the absence of these symptoms is evidence of the purely pigmentary character of the jaundice is based upon a false assumption, for King and Stewart have shown that it is, in fact, upon the bile pigment, that bradycardia depends.

It is at the moment impossible to form a definite opinion upon this question. While all recognize the hæmolysis as the remote cause of the jaundice, the majority of observers still cling to a point of view similar to that of Vaquez and Aubertin, which has been well summarized by Chalier. According to this the condition represents "a lesion of the blood of unknown cause terminating in destruction of the red blood corpuscles, in secondary splenic hyperplasia with the formation of an excess of iron-containing pigment and an overproduction of bile by the liver as a result of the superabundance of pigment to transform, and, consecutively jaundice." In their own words (Vaquez and Aubertin), " . . . . if the primary cause of hæmolytic jaundice is in an alteration of the blood, its immediate cause is without doubt an increased functional activity of the liver cell: there may exist, indeed, a biliary over-activity of the liver just as there exists a glycogenic over-activity of the liver, and hæmolytic icterus would then be an icterus through hepatic over-activity (*'ictère par hyper-hépatie'*)." Their idea as to the manner in which the bile pigment enters the blood is doubtless similar to that expressed by Lcuret, "With the blood pigment modified by the spleen the hepatic cell proceeds to produce an excess of bilirubin to a degree such that in certain cases it overflows and secretes bile at both poles: whence hepatogenous icterus"—essentially the idea of Minkowski. The question must be regarded as still open, and there is much that would attract one to the hæmatogenous hypothesis of Widal, the argument in favor of this point of view being set forth strongly in the thesis of Troisier.

3. As to the third question, the primary cause of the corpuscular fragility, a positive answer cannot be given.

In congenital hæmolytic jaundice it has generally been assumed that the fragility of the red blood corpuscles is an inherited defect. The red cell, it might be fancied, has here failed to acquire those powers of resistance which are ordinarily gained in the first days of extra-uterine life, retaining permanently its original fragility. In the acquired forms of the disease the question is, however, by no means so simple. Widal, Abrami and Brulé, by intra-peritoneal injections of toluylendiamin, have produced in animals a jaundice with clinical and pathological phenomena similar to those observed in hæmolytic jaundice in the human being. According to the dose, the process was more acute and severe, or slower and more gradual and persisting for a long period after the last injection of the poison. No hæmolytic properties could be found in the serum. On the other hand the red blood corpuscles showed a markedly diminished resistance to hypotonic saline solutions as well as a granulation on vital staining, while evidences of increased marrow activity were striking. The urine in some of these cases, however, contained bile pigment. Obstructive jaundice in animals results neither in anæmia, granular corpuscles, nor increased fragility. Indeed, the resistance of the red blood corpuscles is always normal or increased. Here, then, is a similar phenomenon produced primarily by a soluble toxic substance, and while in many instances in the human being, no such cause is apparent, in other cases, such as those occurring in malaria, syphilis and uncinariasis, the primary action of some circulating toxic substance would appear to be certain. It may be, as suggested by Widal, that the marrow, constantly called upon, ends by producing corpuscles less resistant than the normal. But under such circumstances we must fancy that some poisons have acted primarily on blood or marrow. What these may be we know not. The fever associated with paroxysmal aggravations in some cases of acquired hæmolytic jaundice is suggestive of an infection.

It is possible, then, that the corpuscular fragility as well as the granular corpuscles, the main stigmata of the syndrome, may sometimes be secondary to the action of some circulating toxic substance or substances.

Treatment.—Various essays have been made in the treatment of both congenital and acquired hæmolytic jaundice. Widal and his pupils have shown clearly that the persistent administration of iron is the one method from which good

results may be obtained. In the severe acquired forms rest in bed and the other adjuvants suitable for the treatment of any grave anæmia should be adopted. In congenital hæmolytic jaundice recovery is unknown, but a temporary improvement in the anæmia may be obtained by persistent treatment with iron. In acquired hæmolytic jaundice long continued treatment may result in apparent, perhaps, indeed, in complete recovery (Widal, Abrami and Brulé). This is a very important fact when one reflects upon the futility of treatment with iron in Addisonian anæmia, a malady which may so closely resemble this syndrome.

* * * * *

The studies, then, of the last several years have brought out a fairly definite clinical syndrome, that of acholuric jaundice associated with splenomegaly and fragility of the red blood corpuscles. In its purest form this group of symptoms is manifested in a sharply defined disease picture, congenital, often familial splenomegalic jaundice. It is probable that many of Gilbert's cases of chronic simple jaundice with splenomegaly as well as of Hayem's infectious splenomegalic jaundice are examples of the disease.

A similar condition is, however, not infrequently met with in adult life. In these so-called acquired cases the symptoms are usually considerably more acute and severe than in the congenital malady.

The syndrome has, moreover, been found in a variety of other instances of non-obstructive jaundice associated with various infections or poisons.

What the essential primary element in these cases may be is not at present clear.

Most important for the moment is the recognition of those apparently idiopathic examples of acquired hæmolytic jaundice simulating pernicious anæmia, cholelithiasis, the so-called splenic anæmias, or, indeed, *icterus gravis*—most important because of the fact that the recognition and persistent treatment of some of these cases with iron may bring about a great improvement, and, perhaps, a permanent recovery.

The recognition of this syndrome has opened up again, and in an interesting manner, the question as to the possibility of a purely hæmatogenous jaundice.

The methods of studying the corpuscular resistance necessary for the diagnosis of such cases are, of course, too delicate for use by the busy practitioner, but they may be carried out easily in any well-equipped laboratory. One may hope that a re-investigation of some of the many instances of non-obstructive jaundice by means of these methods of study may help to shed further light upon an interesting field of medicine.

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NOTES ON NEW BOOKS.

Dispensing Made Easy. By WM. G. SUTHERLAND, M. B., revised by F. J. WARWICK, M. B. (*Bristol: John Wright & Sons, 1910.*)

This little work contains a great deal of information especially valuable to the physician who does his own dispensing and to the pharmacist of a hospital or dispensary. There are directions for convenient ways of preparing many solutions and combinations of drugs. A number of formulas are given, many of which are taken from the pharmacopeias of the London hospitals. The book contains many practical points, and for the young practitioner it should prove a useful aid in mastering many of the practical details of prescribing.

Nurses' Handbook of Drugs and Solutions. By JULIA C. STIMSON, R. N., Superintendent of Nurses Harlem Hospital, of Bellevue and Allied Hospitals, New York City. Price $1.00. (*Boston: Whitcomb & Barrows, 1910.*)

It is very difficult to write a good textbook for nurses, and this one should, it seems to us, be merely used as a reference book, like a quiz compend. Too much has been crowded into it, and certain sections should either be omitted, or given in greater detain (*c. g.*, Part V, on Antitoxins, Vaccines, and Sera, with their uses). Such a sentence as the following will not be easily grasped by pupil nurses: "The only real success in securing pro-

tection against, and in the cure of diseases produced by microorganisms, is now known to be based upon the artificial direction of the body's own immunizing ability, by means of removing obstacles to its action, of furnishing the appropriate stimulus when such is lacking, or by the addition to the blood stream of specific substances, which the body itself produces, but not in sufficient quantity to be effective in the production of a state of immunity against the infection under which it is struggling" (p. 68). Some of the "Rules for Solutions" are not expressed as clearly as might be, and in some places the metric system is used, and in others the apothecaries'. The value for nurses of such prescriptions as are given under "Common Formulæ" is problematic, to say the least.

Dawn of the Fourth Era in Surgery and Other Short Articles Previously Published. By Robert T. Morris, A. M., M. D., etc.

The author's many friends and admirers, as well as other students of surgery, will be pleased to have this collection of his papers in a neat and attractive form. Naturally all will not agree with Dr. Morris' dicta on certain surgical points, but his views deserve consideration, and an hour can be well spent rereading these articles, which deal with the use of the rubber glove, the appendix, the gall bladder, rapidity of operation, etc.

Principles of Therapeutics. By A. Manquat, National Correspondent to the Académie de Médicine. Translated by M. Sinbad Gabriel, M. D. Price, $3.00. (*New York and London: D. Appleton & Co., 1910.*)

In this book the author discusses the general principles that underlie the giving of medicines, and the use of other therapeutic agents. It is dedicated to "young physicians," and "every line of it is devoted to *practice*, with the double object of being useful and doing no harm." It is divided into the following twelve chapters: I. Views of the Various Manners of Conceiving Therapeutics; II. The Forms of Therapeutic Action; III. Of the Action of Medicines; IV. Doses; V. Medicinal Opportunity; VI. Primum Non Nocere! VII. The Elements of Therapeutic Individualization; VIII. Influence of Environment on Therapeutic Results; IX. Variations of Therapeutic Activity Inherent in Medicines; X. Non-medicinal Therapeutic Actions; XI. Method in Therapeutics, and XII. Division of Therapeutic Agents. Much good advice is given, but it is not always presented in the happiest form; the author's style is not so lucid as that of many French writers, but those who have time to read this rather diffuse work will benefit themselves. Such clumsy and un-English words as "hyposthenizants," "hyposthenizing," "thermality," "nosocratic," "stomachal" and others mar the text, and the translation of many of the sentences is too literal and awkward. The definition of disease (p. 58) as "*the disturbance of the habitual organic equilibrium by the fact of an abnormal force acting with sufficient intensity to modify the fixity of its reactions, the habitual play of its functions and at times its structure and chemical composition, thus giving rise to disorders which persist until the accomplishment by this living matter of elimination or destruction of the modifying cause or else its own adaptation to the presence of the disturbing force*," may be intelligible in French, but is not readily comprehensible as it stands. "Nutritive movement" (p. 147) for digestion is not happy. In spite, however, of these defects in its English form, the book has value.

An Anatomical and Surgical Study of Fractures of the Lower End of the Humerus. By Astley Paston Cooper Ashhurst, A. B., M. D., etc. The Samuel D. Gross Prize Essay of the Philadelphia Academy of Surgery, 1910. (*Philadelphia and New York: Lea & Febiger, 1910.*)

Illustrated by case histories and excellent photographs and radiographs, this is a valuable monograph, one which every surgeon who sees many fractures will find helpful. The understanding of these fractures has been made clearer by Dr. Ashhurst's experimental and anatomical work. That the study is thorough is shown by the contents which include Introduction, Anatomy, Development of the Lower Epiphysis of the Humerus, Classification, Pathogenesis, Examination of the Patients, Supracondylar Fractures, Transverse, Diacondylar Fractures, Fractures of the External Condyle, Fractures of the Epitrochlea, Epiphyseal Separations, Fractures of the Internal Condyle, Intercondylar Fractures, Complications, Dressing the Elbow in Hyperflexion, Results, and Clinical Histories. The winning of the Samuel D. Gross Prize marks the distinction of this piece of work.

An Introduction to Surgery. By Rutherford Morison, M. A., M. B., F. R. C. S., Edin. and Eng., etc. Illustrated. Price, 8/6. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1910.*)

This work of about 150 pages is divided into ten chapters as follows: (1) Inflammation, (2) Bacteria, (3) Ulcers, (4) Gangrene, (5) Syphilis, Tubercle, and Malignant Disease, (6) Hæmophilia, (7) Wounds, (8) Abdominal and Pelvic Viscera, (9) Indications for Operation, (10) X-rays. It is difficult to understand for whom such a work is intended. Much of the teaching is puerile—it is like a book written in words of one syllable. Students who are not able to grasp more in an Introduction to Surgery, should not begin to study surgery. One poor paragraph on "Leucocytosis," and less than two pages on "Gonorrhœa" should not be considered as proper education to any class of students at any time in their career. Such a book is not really helpful to anyone. It is much too diagrammatic and epigrammatic.

Anæmia. By Dr. P. Ehrlich and Dr. A. Lazarus. Part 1. Volume 1. Normal and Pathological Histology of the Blood. Second Edition. (Enlarged and to a great extent rewritten). By Dr. A. Lazarus and Dr. O. Naegeli. Translated for the German by H. W. Armit, M. R. C. S., L. R. C. P. (London). Illustrated. Price, $4.00. (*New York: Rebman Company, 1910.*)

The new edition of this well-known work will be welcome to all hæmatologists and clinicians. Ehrlich's studies of the blood are fundamental, and every student of this branch of medicine must be acquainted with them. This translation will, therefore, be of great help to those who are unable to read the original book in German. It is divided into four chapters. Chapter 1, Introduction; Definition—Clinical Methods of the Examination of Blood; and Chapter II, The Morphology of the Blood, are by Dr. Lazarus; Chapter III, The White Blood Corpuscles, by Dr. Naegeli; and Chapter IV, The Blood Platelets: The Hæmoconia, by Dr. Lazarus.

Applied Anatomy. The Construction of the Human Body Considered in Relation to Its Functions, Diseases and Injuries. By Gwilym G. Davis, M. D., Associate Professor of Applied Anatomy, University of Pennsylvania, etc. With 630 illustrations, mostly from original dissections and many in color, by Erwin F. Faber. (*Philadelphia and London: J. B. Lippincott Company.*)

Any thorough work which will aid the medical student to overcome the feeling that anatomy is a dull, dry subject, and has little practical relation to medicine, is welcome, and he who, along with his Gray, will read his Davis, will find that, after all, human anatomy is a living subject, and will be helped through many a tedious hour. The aim of the author "is to show the relation of structure to function" in both normal and pathological conditions, and with a clear text and abundance of illustrations, he has produced a really valuable book, which can be said of very few

modern medical works. The book is intended not alone for students, but surgeons and physicians will often find occasion to turn to its pages for information or the solution of some difficult problem. It is well arranged, and satisfactory in every way, except for its weight, excusable only by the handsome paper used.

Clinical Pathology in Practice, with a Short Account of Vaccine Therapy. By THOMAS J. HORDER, M. D., R. R. C. P., etc. Price, $3.00. (*London: Henry Frowde* and *Hodder & Stoughton, 1910.*) Oxford Medical Publications.

"The aim of this book is to present the practitioner with a brief survey of the scope and usefulness of modern pathological methods as applied to the diagnosis and treatment of disease. It is not intended to serve as a laboratory text-book . . . ." Such is the limitation of the book that many another laboratory text-book along these same lines is more useful to the student, since the practice of clinical pathology should go hand in hand with the theory of its use. After three preliminary chapters (Introductory, The Collection of Materials, Blood Culture) the author takes up The Histological Examination of the Blood, The Sputum, Pleural, Lung, Lumbar and Joint Puncture, Infective Conditions of the Nose, Mouth, Throat, and Urinary Tracts, Examination of the Fæces, the Diagnosis of Tuberculosis and Its Specific Treatment, Certain Specific Serum Tests and Their Value in Diagnosis, Fever without Other Physical Signs, and Vaccine Therapy. Simply and only as an introduction to the further study of these subjects can this book serve a purpose, and that rather inadequately.

A Manual of Nursing. By MARGARET FRANCES DONAHOE, formerly Superintendent of Nurses and Principal of Training School, Philadelphia General Hospital. Illustrated. (*New York and London: D. Appleton & Co., 1910.*)

This "Manual" covers all nursing and, therefore, is more complete than some of the treatises on this subject. On the whole, it is satisfactory, but it lacks distinction. The difference between a primary text-book on medicine and a treatise on nursing is not kept clearly in mind by the authoress, and this detracts from the value of the book, for some of her remarks in the chapter on the nursing of contagious diseases are not always correct. Throughout the work there are statements which need revision, but there are few errors of real consequence, and nurses will not be led far astray in reading this book, though they could spend their time better on some others.

International Clinics. Edited by HENRY W. CATTELL, A. M., M. D., with collaborators. Vol. IV. Twentieth Series, 1910. (*Philadelphia and London: J. B. Lippincott Company.*)

This volume opens with a timely article on "606" by the editor. It is important that the value and use of this new remedy should be thoroughly understood by the profession, and this article will be of material aid. Dr. J. J. Walsh has written another one of his entertaining and instructive historical papers on the "Physicians' Fees Down the Ages," and there are numerous other clinics on "Diagnosis and Treatment," "Medicine," "Surgery," "Neurology," "Pathology," "Ophthalmology," "State Medicine," and "Postgraduate Course," which will please and satisfy a variety of readers.

Studies in Invalid Occupation. A Manual for Nurses and Attendants. By SUSAN C. TRACY. Price, $1.50. (*Boston: Whitcomb & Barrows, 1910.*)

This is an excellent and most helpful work for the classes to whom it is addressed. The descriptions of objects to be made by the patients are clear, and there are a number of photographs and drawings which are also useful. To keep the hands of invalids with mental troubles of one sort and another, occupied is one of the most important means of curing them, and in any case, of preventing their mental condition becoming worse. Manual exercises of all kinds are an excellent means of keeping the minds of normal people healthy, and are still more important for the abnormal, and as an aid to all who care for those with mental disturbances this book can be heartily commended. Few attendants have sufficient imagination or knowledge to get on without a guide of this sort, and the majority will be glad of the assistance to be found in these "Studies."

A System of Syphilis in Six Volumes. Edited by D'ARCY POWER, M. B., Oxon., F. R. C. S., and J. KEOGH MURPHY, M. D., F. R. C. S. With an introduction by JONATHAN HUTCHINSON, F. R. S. Vol. II. (*London: Henry Frowde and Hodder & Stoughton, 1908.*) Oxford Medical Publication.

The editor-in-chief, Dr. D'Arcy Power, opens this volume with an interesting and able paper on the "Surgery of Syphilis," and he is followed by Col. F. J. Lambkin, who contributes two noteworthy papers on "The Treatment of Syphilis," and "An Outbreak of Syphilis in a Virgin Soil." The final chapter on "Syphilis in Obstetrics" is well handled by Dr. William J. Gow. Since the appearance of this volume two years ago the new method of treating syphilis with "606" has been discovered, but this remedy will not altogether drive out of use or supplant the older ones, so that Col. Lambkin's paper on treatment is still well worth reading and studying. There is no doubt that for all students of syphilis this is a most important system, and each volume contains papers of exceptional value. Such experiences as Col. Lambkin had with this disease in Uganda are exceedingly rare and of the greatest interest. The volume is illustrated with some beautiful color reproductions.

American Practice of Surgery. A Complete System of the Science and Art of Surgery. By Representative Surgeons of the United States and Canada. Editors: JOSEPH D. BRYANT, M. D., LL. D.; ALFRED H. BUCK, M. D. Complete in eight volumes, profusely illustrated. Vol. VI. (*New York: William Wood & Co., 1909.*)

The surgeons, who contribute articles to this volume, are: Armstrong, Elder and Shepherd, of Montreal; Balch, Cabot, Graves and Mosher, of Boston; Carson and Mudd, of St. Louis; Bloodgood, of Baltimore, and Turner, of Philadelphia. Unless one turns to the individual articles there is no means of quickly finding the respective authors, whose names might have readily been placed after the subject headings under "Contents." Bloodgood's paper on the "Surgical Diseases of the Jaws" is separated from other papers on the surgery of the face and throat by a number of papers on the surgery of the female and male genitals. These are minor defects, but in a well-arranged system they would not occur. The very completeness of this sytem leads to redundancy of material. The volume opens with a paper on Prosthesis in its Relation to Surgery of the Face, Mouth, Jaws and Nasal and Laryngeal Cavities, followed in sequence by chapters on Surgical Diseases and Wounds of the Nasal Cavities and Accessory Sinuses; Surgical Diseases and Wounds of the Mouth, Tongue, and Salivary Glands; Surgical Diseases and Wounds of the Neck; Surgical Diseases and Wounds of the Thyroid and Thymus; Surgery of the Thorax and Spinal Column; Surgical Diseases and Wounds of the Female Breast; Surgical Diseases and Wounds of the External Genitals and Vagina of the Female; Surgical Diseases and Wounds of the Male Genital Organs; Chancroid; Gonorrhœal Urethritis, and Surgical Diseases and Wounds of the Jaws. Thus these articles take up 900 pages and the volume is so heavy as to be unwieldy. There are but few references, which seems rather a defect in a classical work of this nature, but the question of mul-

tiple references is a debated one. Many of the drawings and photographs are excellent, but the colored plates are not good. The articles, on the whole, cover the ground well, and the surgeon in need of this system will find it a useful book. This volume may be said to well uphold the repute already gained by American and Canadian surgeons, and while there is no paper of exceptional merit in this volume, the general average of excellence is high.

Hydrotherapy. A Work on Hydrotherapy in General, Its Application to Special Affections, The Technic or Processes Employed and the Use of Waters Internally. By Guy Hinsdale, A. M., M. D., etc. Illustrated. Price, $3.50. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

A few years ago the number of text-books on this subject was limited, but they are now constantly increasing in numbers, and there is no longer any reason why the general practitioner should not have a clear idea of the uses and value of water applied both internally and externally. The best part of most of these text-books is the description of the technic in giving the different forms of baths and sprays. The authors have a tendency, it seems to us, to exaggerate the value of water in many affections, but it must be said that those who do not use hydrotherapy freely do not recognize its many values. This work is a smaller one than Kellogg's, and sufficient for the use of the ordinary practitioner. The chapter on the use of baths in typhoid fever, where correct use of water is so important, is, however, most unsatisfactory, it is far too brief, and the author should have given a fuller account of their action, and when they should and should not be given.

It is a pity to add to our medical terms such words as "Crounotherapy" and "Crenology," which are really not needed, and the same figure with slightly different description is given on pages 73 and 245.

The Mental Symptoms of Brain Diseases—An Aid to the Surgical Treatment of Insanity, Due to Injury, Hæmorrhage, Tumors and Other Circumscribed Lesions of the Brain. By Bernard Hollander, M. D. With Preface by Dr. Jul. Morel. Price $2. (*New York: Rebman Company, 1910.*)

In this work the author has classified a large number of cases taken from the literature under lesions of the different lobes depending on the nature of the symptoms shown. Under lesions of the frontal lobes he groups cases where the higher intellectual operations or the centers of perception and special memories or the higher human sentiments seem to be most affected. Cases of melancholia are grouped under lesions of the parietal lobes; and others of violent and homicidal mania fall under lesions of the temporal lobes, and so on. Such a classification as all neurologists know cannot be exact, for symptoms are not always clear cut, but one group shades into another, and an exact diagnosis of the site of the lesion cannot be made. The book, if used with thought, may, however, be helpful as a guide to students in their earlier studies of brain lesions.

BOOKS RECEIVED.

A Text-Book of Bacteriology. A Practical Treatise for Students and Practitioners of Medicine. By Philip Hanson Hiss, Jr., M. D., and Hans Zinsser, M. D. With one hundred and fifty-six illustrations in the text, some of which are colored. 1910. 8vo. 745 pages. D. Appleton and Company, New York and London.

Diseases of Infants and Children. By Edmund Cautley, M. D., Cantab., F. R. C. P. Lond. 1910. 8vo. 1042 pages. Paul B. Hoeber, New York.

The Sexual Disabilities of Man and Their Treatment. By Arthur Cooper. Second edition, revised and enlarged. 1910. 16mo. 204 pages. Paul B. Hoeber, New York.

Urinary Surgery. A Review. By Frank Kidd, M. D., B. C. (Cantab.), F. R. C. S. 1910. 8°. 429 pages. Longmans, Green and Company, London, New York, Bombay and Culcutta.

Phases of Evolution and Heredity. By David Berry Hart, M. D., F. R. C. P. E. 12mo. 259 pages. Rebman Company, New York.

The Principles and Practice of Medicine. By William Osler, M. D., F. R. S. Seventh edition. Translated by Philip B. Cousland, M. B., C. M., Edin. 1910. 8vo. Publication Committee, China Medical Missionary Association, Shanghai.

An Anatomical and Surgical Study of Fractures of the Lower End of the Humerus. By Astley Paston Cooper Ashhurst, A. B., M. D. The Samuel D. Gross Prize Essay of the Philadelphia Academy of Surgery, 1910. 8vo. 163 pages. Lea & Febiger, Philadelphia and New York.

A Manual of Nursing. By Margaret Frances Donahoe. Illustrated. 1910. 12mo. 489 pages. D. Appleton and Company, New York and London.

Report of the Surgeon-General, United States Army, to the Secretary of War, 1910. Annual Reports, War Department. Fiscal year ended June 30, 1910. 8vo. 223 pages. Government Printing Office, Washington.

Recherches d'Anatomie Chirurgicale sur les Artères de l'Abdomen; Le Trona Coelicque. Par Pierre Descomps. 1910. 4°. 205 pages. G. Steinheil, Paris.

Eléments d'Anatomie Pathologique. Par L. Bériel. Avec 232 figures dessinées par le l'auteur. 8vo. 563 pages. G. Steinheil, Paris.

Urgent Surgery. By Félix Lejars. Translated from the sixth French edition by William S. Dickie, F. R. C. S. With 20 full-page plates and 994 illustrations, of which 602 are drawn by Dr. E. Daleine and A. Leuba, and 217 are from original photographs. Vol. II. The Genito-Urinary Organs—The Rectum and Anus—the Strangulated Hernias—the Extremities. 1910. 4to. 580 pages. William Wood and Company, New York.

The Mental Symptoms of Brain Diseasc. An Aid to the Surgical Treatment of Insanity, due to Injury, Hæmorrhage, Tumors and other Circumscribed Lesions of the Brain. By Bernard Hollander, M. D. With preface by Dr. Jul. Morel. [1910.] 12mo. 237 pages. Rebman Company, New York.

The Modern Treatment of Alcoholism and Drug Narcotism. By C. A. McBride, M. D., L. R. C. P. & S. (Edin.) [1910]. 12mo. 376 pages. Rebman Company, New York.

Hints for the General Practitioner in Rhinology and Laryngology. By Dr. Johann Fein. Translated by J. Bowring Horgan, M. B., B. Ch. With forty figures in the text and two photographic plates. [1910.] 12mo. 223 pages. Rebman Company, New York.

Anæmia. By Geh. Obermedizinalrat Professor Dr. P. Ehrlich and Dr. A. Lazarus. Volume 1. Part 1. Normal and Pathological Histology of the Blood. Second edition (enlarged and to a great extent rewritten), by Dr. A. Lazarus and Dr. O. Naegeli. Translated from the German by H. W. Armit, M. R. C. S., L. R. C. P. (London). With 5 illustrations in the text and 5 colored plates. 1910. 8vo. 218 pages. Rebman Company, New York.

Diagnosis and Treatment of Diseases of Women. By Harry Sturgeon Crossen, M. D. Second edition, revised and enlarged. With seven hundred and forty-four engravings. 8vo. 1025 pages. C. V. Mosby Company, St. Louis.

Nursing Made Easy. With Numerous Formulæ, and Practical Hints to Secure Simplicity, Rapidity and Economy. By Wm. C. Sutherland, M. B. Aberd. Fourth edition, revised by F. J. Warwick, B. A., M. B. Cantab., M. R. C. S., L. S. A. 1910. 16°. 102 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent and Co., Ltd., London.

The Diseases of China, Including Formosa and Korea. By W. Hamilton Jefferys, A. M., M. D., Univ. of Pennsylvania, and James L. Maxwell, M. D. London. With 5 colored plates, 11 nosogeographical plates, and 360 illustrations in the text. 1910. 8vo. 716 pages. P. Blakiston's Son & Co., Philadelphia.

Modern Treatment. The Management of Disease with Medicinal and Non-Medicinal Remedies. In Contributions by American and Foreign Authorities. Edited by Hobart Amory Hare, M. D. Assisted by H. R. M. Landis, M. D. In Two Volumes. Volume I. Illustrated. 1910. 8vo. 930 pages. Lea & Febiger, Philadelphia and New York.

The Racial Anatomy of the Philippine Islanders. Introducing New Methods of Anthropology and Showing their Application to the Filipinos with a Classification of Human Ears and a Scheme for the Heredity of Anatomical Characters in Man. By Robert Bennett Bean, B. S., M. D. With nineteen illustrations reproduced from original photographs. Seven figures. 1910. 8vo. 236 pages. J. B. Lippincott Company, Philadelphia and London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume IV. December, 1910. 8vo. 360 pages. Lea & Febiger, Philadelphia and New York.

Scientific Memoirs. New Series, No. 38. By Officers of the Medical and Sanitary Departments of the Government of India. *Preliminary Report on the Killing of Rats and Rat Fleas by Hydrocyanic Acid Gas.* By Captain W. D. H. Stevenson, M. B., I. M. S. 1910. Fol. 28 pages. Superintendent Government Printing, Calcutta, India.

An Introduction to Surgery. By Rutherford Morison, M. A., M. B., F. R. C. S. Edin and Eng. With 146 illustrations in the text, and 5 colored plates. 1910. 4to. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

Practical Bacteriology, Blood Work and Animal Parasitology. Including Bacteriological Keys, Zoological Tables and Explanatory Clinical Notes. By E. R. Stitt, A. B., Ph. G., M. D. Second edition, revised and enlarged with 91 illustrations. 1910. 12°. 345 pages. P. Blakiston's Son & Co., Philadelphia.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Volume IV. Twentieth Series, 1910. 8vo. 308 pages. J. B. Lippincott Company, Philadelphia.

Principles of Therapeutics. By A. Manquat. Translated by M. Simbad Gabriel, M. D. 1910. 8vo. 298 pages. D. Appleton and Company, New York and London.

Clinical Pathological in Practice. With a Short Account of Vaccine-Therapy. By Thomas J. Horder, B. Sc., M. D., F. R. C. P. 1910. 8vo. 216 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Puerperal Infection. By Arnold W. W. Lea, M. D., B. S. (Lond.), B. Sc. (Manch.), F. R. C. S. (Eng.). 1910. 8vo. 384 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Induced Cell-Reproduction and Cancer. The Isolation of the Chemical Causes of Normal and of Augmented, Asymmetrical Human Cell-Division. By Hugh Campbell Ross, M. R. C. S. (Eng.), L. R. C. P. (Lond.). Being the results of researches carried out by the author with the assistance of John Westray Cropper, M. B., M. Sc. (Liv.), M. R. C. S. (Eng.), L. R. C. P. (Lond.). With 129 illustrations. 1911. 8vo. 423 pages. P. Blakiston's Son & Co., Philadelphia.

Emanuel Swedenborg's Investigations in Natural Science and the Basis for His Statements Concerning the Functions of the Brain. By Martin Ramström. 1910. 4to. 59 pages. University of Upsala.

Studies in Invalid Occupation. A Manual for Nurses and Attendants. By Susan E. Tracy. 1910. 8vo. 175 pages. Whitcomb & Barrows, Boston.

Nurses Handbook of Drugs and Solutions. By Julia C. Stimson, R. N. 1910. 12°. 82 pages. Whitcomb & Barrows, Boston.

A Text-Book of General Bacteriology. By Edwin O. Jordan, Ph. D. Second edition, thoroughly revised. Fully illustrated. 1910. 8vo. 594 pages. W. B. Saunders Company, Philadelphia and London.

The Practice of Surgery. By James Gregory Mumford, M. D. With 682 illustrations. 1910. 8vo. 1015 pages. W. B. Saunders Company, Philadelphia and London.

Hydrotherapy. A Work on Hydrotherapy in General, its Application to Special Affections, the Technique or Processes Employed, and the Use of Waters Internally. By Guy Hinsdale, A. M., M. D. Illustrated. 1910. 8vo. 466 pages. W. B. Saunders Company, Philadelphia and London.

Treatise on Diseases of the Skin. By Henry W. Stelwagon, M. D., Ph. D. Sixth edition, thoroughly revised. With 289 illustrations in the text, and 34 full-page colored and half-tone plates. 1910. 8vo. 1195 pages. W. B. Saunders Company, Philadelphia and London.

Dawn of the Fourth Era in Surgery. And Other Short Articles Previously Published. By Robert T. Morris, A. M., M. D. 1910. 12°. 145 pages. W. B. Saunders Company, Philadelphia and London.

Transactions of the American Gynecological Society. Volume 35. For the year 1910. 8vo. 566 + LXII pages. Philadelphia.

Transactions of the Congress of American Physicians and Surgeons. Eighth Triennial Session held at Washington, D. C., May 3 and 4, 1910. 8vo. 456 pages. Published by the Congress, New Haven, Conn.

The Harvey Lectures. Delivered Under the Auspices of the Harvey Society of New York, 1909-1910. By Prof. Richard M. Pearce, Prof. Otto Cohnheim, Prof. T. G. Brodie, Prof. G. Carl Huber, Prof. Ludwig Hektoen, Prof. Eugene L. Opie, Prof. Adolf Meyer, Prof. A. Magnus-Levy. 1910. 8vo. 276 pages. J. B. Lippincott Company, Philadelphia and London.

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CLINICAL NOTES.*

(1) INTERMITTENT FEVER IN INFLUENZA SIMULATING MALARIAL FEVER. (2) GRAVE MALARIAL FEVER WITH FEW PARASITES IN THE PERIPHERAL CIRCULATION. DANGERS OF THE INTRAVENOUS INJECTION OF QUININE.

By William Sydney Thayer, M. D.,

Associate Physician, The Johns Hopkins Hospital, Baltimore.

Every one who has observed much malarial fever is familiar with the fact that well-marked paroxysms may occur with the presence of very few parasites in the peripheral circulation. (a) This is not uncommon in mild tertian infections. (b) Furthermore, it is observed at the onset of mild and even of more or less serious æstivo-autumnal fever, especially during the period of the paroxysm. The cause of this is evident enough when we remember that the sporulation of the parasites which immediately precedes and accompanies the paroxysm in both tertian and æstivo-autumnal fever, occurs, especially in capillaries of certain of the internal organs, particularly in the spleen and bone marrow. In most mild cases of æstivo-autumnal fever, it is rather difficult to find sporulating parasites in the peripheral circulation. (c) The same condition, *i. e.*, well-marked fever with few or no parasites demonstrable in the peripheral circulation, is seen in both tertian and æstivo-autumnal infections, but, especially in the latter, where quinine has been given in insufficient doses early in the attack.

In most patients, careful examination of blood reveals parasites within the twenty hours succeeding the paroxysm, and, even in the absence of parasites, the diagnosis is usually sufficiently clear through the history of the case and the physical appearances, in connection with the condition of the blood which shows usually (1) leucopenia, (2) pigment-bearing leucocytes, (3) a relative increase in the large mononuclear leucocytes.

Nevertheless, it is well known that there are occasional cases in which, without splenic puncture, a diagnosis can be reached only by the therapeutic test. These cases are not common and,

* Remarks made before the Johns Hopkins Hospital Medical Society on Oct. 17, 1909.

in a community where a study of blood is a part of the routine examination, as it is here, where one usually waits for the demonstration of parasites before the administration of quinine, it is easy to lay too much stress on the negative results

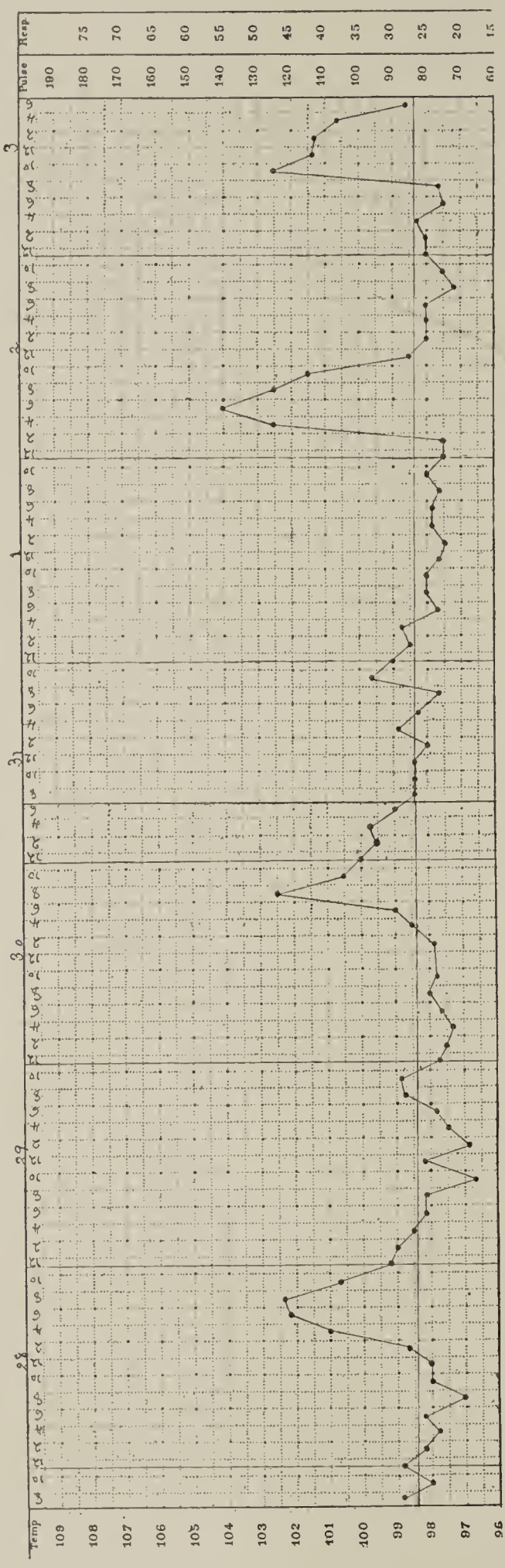

Chart I.—Influenza.

of such examinations and to forget that grave and even pernicious malaria may occur in an individual with so few parasites in the peripheral circulation as to deceive even the skilled observer on repeated examinations.

On the other hand, however, 'tis very important to remember that certain other infections may give rise to paroxysms which, intrinsically, and in the character of their periodicity, may closely simulate malaria.

The paroxysms of streptococcus, pneumococcus and gonococcus septicæmia are usually distinguishable by the irregularity, often the great frequency of the paroxysms, and the short duration of the individual access. The paroxysms occurring in tuberculosis may often suggest malaria, but are usually readily distinguishable. In the experience of the writer, influenza is the malady which gives rise to those forms of intermittent fever which most closely simulate malarial paroxysms. Of the four cases of which we shall speak this evening, two are examples of influenza simulating malaria; two are instances of grave malarial fever with a remarkable paucity of parasites in the peripheral circulation.

Case I.—*Influenza—Tertian Paroxysms Simulating Malaria.* The first chart, which has already been published in my "Lectures on the Malarial Fevers," * is that of a woman, E. D., aged 29, who was a patient on Ward "G" of the Johns Hopkins Hospital. The chart, as you will see, shows a febrile paroxysm beginning between 2 and 4 p. m., on the 28th of January and lasting 12 hours. This was succeeded on the 30th by a similar paroxysm beginning about two hours later and lasting about the same length of time. The patient came from a malarious district and we naturally suspected a tertian infection. On the first of February, however, there was no rise of temperature and on the 2d and 3rd, sharp elevations occurred, one between 12 and 2 in the morning and the other between 8 and 10 on the following morning. These latter paroxysms, of course, would be sufficient, on examination of the chart alone, to render the diagnosis of malaria improbable.

Now, this patient complained of coryza and cough with a greenish purulent expectoration, and showed the signs of a general bronchitis. Examination of the blood revealed no malarial organisms, and a leucocytosis of 17,000. Influenza bacilli were cultivated from the sputa and the patient recovered without relapse, and without the administration of quinine.

Case II.—*Influenza—Remittent and Intermittent Fever Simulating Malaria.* The second chart is that of a patient whom I saw in February, 1907, with Dr. Friedenwald. As you will see, there is a period of four days of irregular fever, followed by three quotidian paroxysms, each beginning between 8 and 10 in the morning and closely simulating paroxysms of a regularly intermittent malaria. One might well have fancied that the case represented one of infection with mutiple groups of parasites which, under rest in bed, had gradually given way until the effects of two strong groups became clearly evident.

The patient, however, was a boy of about 17 who had been ill for about three or four days before the beginning of the chart, complaining of coryza and cough with purulent expectoration and the general symptoms of influenza which was prevalent at the time. From the onset, he had been treated with quinine, gr. iii. (0.2 gm.) every four hours. Well-marked chills continued for nearly a week after the onset of treatment. The blood showed no malarial parasites.

I saw the patient first on the 14th of February, at which time he showed a general bronchitis. Quinine was omitted and aspirin, gr. v. (0.325 gm.) every four hours ordered. Cultures from the sputa showed *B. influenzæ.*

The point of special interest in this case would appear to be the sharpness of the paroxysms which were associated with definite

* Thayer, W. S.: Lectures on the Malarial Fevers, New York, D. Appleton & Co., 1897.

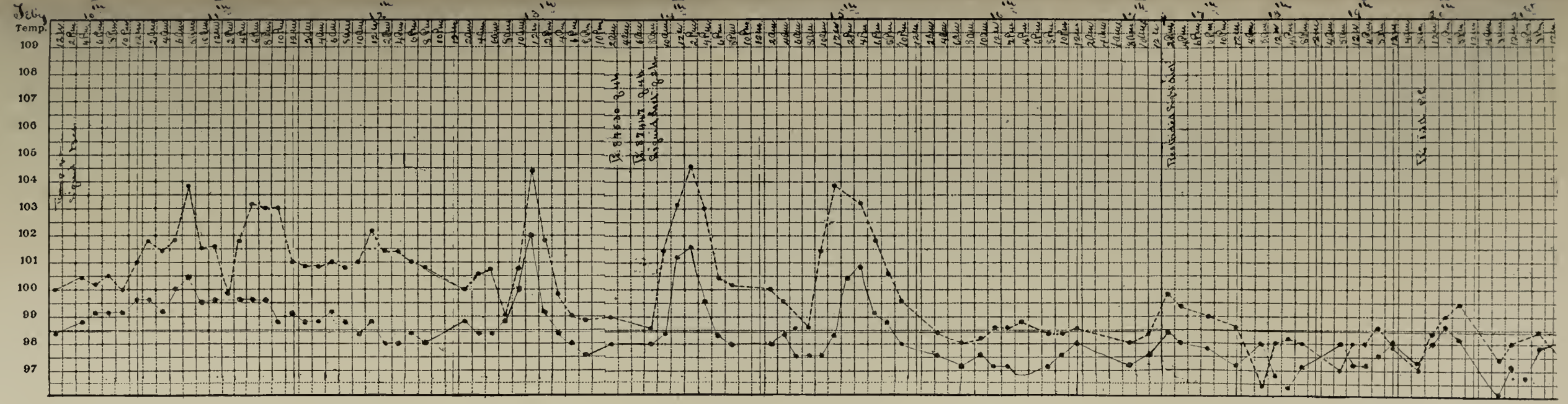

CHART II.—INFLUENZA.

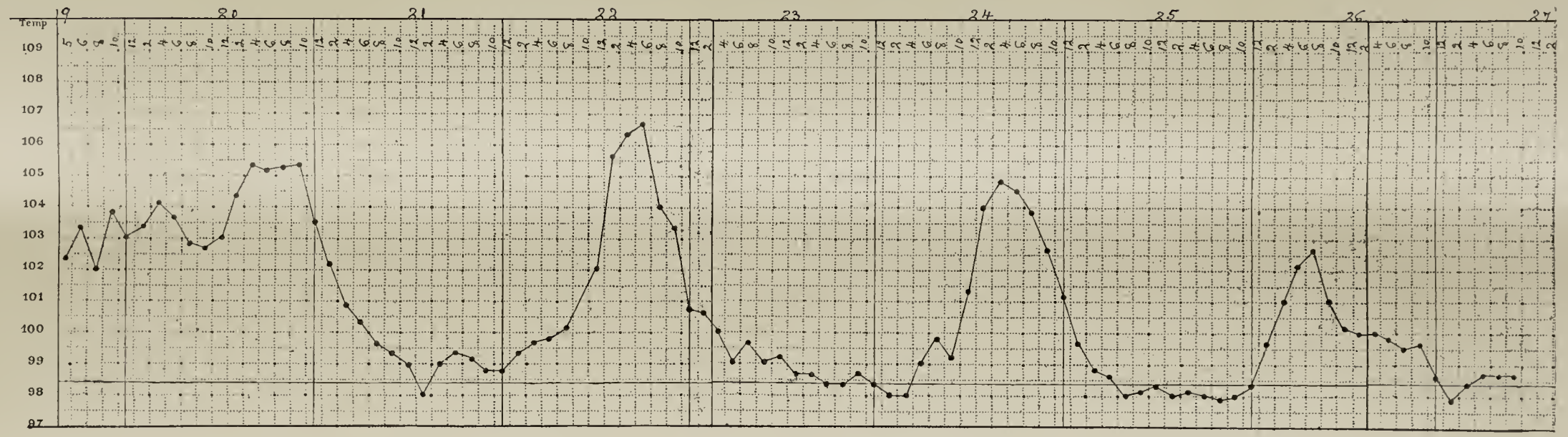

CHART III.—MALARIAL FEVER, ÆSTIVO-AUTUMNAL TERTIAN.

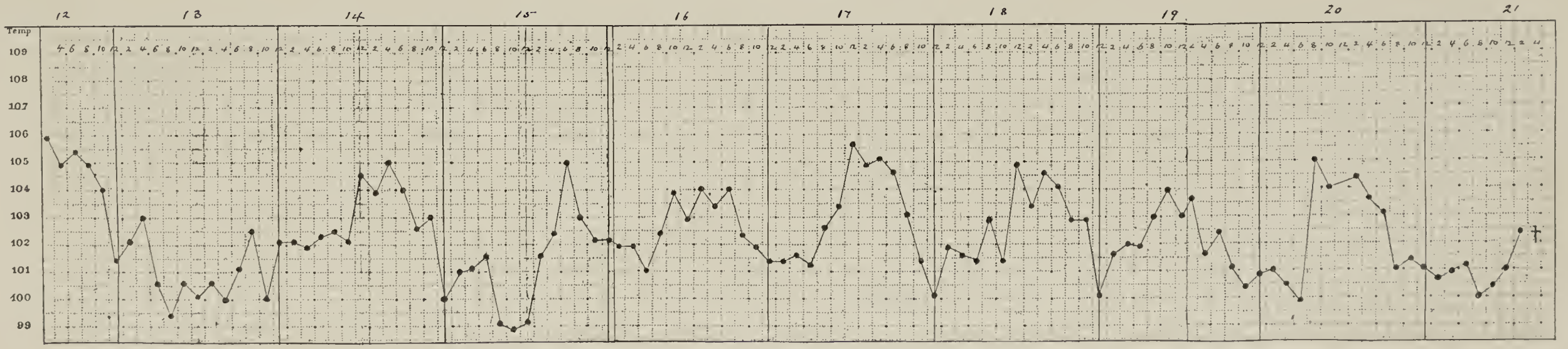

CHART IV.—MALARIA.—ÆSTIVO-AUTUMNAL TERTIAN.

chills, and the regularity of their onset in the morning hours, as is common in malaria.

Case III.—*Intermittent Fever of the Type of Aestival Tertian. No Parasites Demonstrable in the Peripheral Circulation. Immediate Disappearance of Fever under Quinine.* The third chart that I would show you presents a rather different appearance. As you will see, there is continued fever on the 19th and 20th of October, the temperature reaching a sub-normal point on the 21st. This is followed by sharp paroxysms on the 22d, 24th, and 26th, the paroxysms beginning in the early morning hours and lasting nearly 24 hours. The chart is typical of aestivo-autumnal tertian fever.

The patient was a medical student of 28. He had been in a malarious district and, two days before admission, had begun to complain of general malaise and on the day preceding admission, of fever. On the day of admission, the 19th of October, he had taken three doses of quinine, how much is not known. On entrance, the temperature was 102.4° F. at 5 P. M., the pulse 80, respiration 24. There was nothing striking on physical examination of the patient beyond a palpable spleen which extended 3 cm. below the costal margin. The examination of the blood was negative; no parasites and no pigment were seen and the leucocytes were 6400 per cmm.

Oct. 20. The temperature remained elevated. In the afternoon, there was a chill and the temperature rose to 105.8° F.; leucocytes, 4640.

Oct. 21. The temperature fell gradually to 98° F. at noon.

Oct. 22. There was a sharp rise in temperature with a chill at about 6 p. m., the temperature reaching 106.7° F. This was followed by a rapid fall, and, on Oct. 23, the temperature was normal.

On Oct. 24, the temperature rose slightly in the early morning hours, a sharp paroxysm beginning at 8, with a chill at noon, during which the temperature rose to 105° F. During all these days, the blood was carefully and repeatedly examined in both fresh and stained specimens. Neither parasites nor pigment was to be found and the leucocytes diminished to between 3,000 and 4000 per cmm.

At 8 p. m., on the 24th, quinine sulphate gr. x (0.65 gm.) every four hours was ordered.

On the 25th, the temperature was normal.

Early in the morning of the 26th, there was a slight paroxysm, much less intense than the preceding but lasting a full 24 hours. After this, the temperature remained permanently normal. Quinine was continued for a long period of time and there was no relapse. Repeated examinations of blood showed no parasites whatever and no pigment.

Now, the history of this case, the time of the year at which it occurred, the character of the febrile curve, the palpable spleen, the leucopenia and the apparently specific action of quinine, leave no serious doubt in one's mind that this was a case of malaria, probably æstivo-autumnal.

This is the first case in the history of the hospital in which we have been obliged to resort to the therapeutic test for the proof of the existence of a malarial infection.

Splenic puncture would probably have assisted us materially in the diagnosis. This was not performed because of the danger, minimal though it be. I have, myself, aspirated many spleens without the slightest trouble, and, in any case of emergency, I should have no hesitation in so doing again. Some years ago, however, I witnessed a fatal result of splenic puncture. The patient was a foreigner, unable to understand English. He failed to comprehend the procedure and jumped on the introduction of the hypodermic needle. This resulted in a small tear of the splenic capsule with fatal hæmorrhage into the peritoneal cavity. Although I feel convinced that with proper precaution, the danger is almost *nil*—and this has been the experience among more careful Italian observers, one of whom Prof. Bastianelli, is with us this evening, yet I cannot feel that splenic puncture is justified excepting in cases of real necessity.

It is interesting that Ruge * makes the surprising statement that "the mortality from splenic puncture, which has been observed up to the present time, amounts to 1½ per cent."

It is highly probable that the early administration of quinine was in this case responsible firstly, for the development of the regular paroxysms; secondly, for the disappearance of parasites in the peripheral circulation.

Case IV.—*Grave Æstivo-Autumnal Tertian Fever. Remarkable Paucity of Parasites in the Peripheral Circulation. Convulsions and Death Following the Subcutaneous Injection of Quinine.*—In addition to these three cases, I would speak of another patient whose history is remarkable from various standpoints. The chart, as you will see, shows that which on first appearance appears to be a wholly irregular remittent fever. There are, however, certain very sharp remissions while many of the smaller oscillations are dependent upon the administration of baths. A careful study of the chart shows that every other day (on the 14th, 16th, 18th and 20th of October) there was a sharp rise of temperature somewhere between 6 and 10 a. m. This is followed by a remission during the afternoon and night and a second rise on the following day with a fall occurring in the afternoon or evening. In other words, the chart suggests the pseudo-crisis and subsequent elevation first described in æstivo-autumnal tertian fever by the Italian observers. Such a chart might well suggest an æstivo-autumnal tertian.

This patient was a sailor on a bay boat, a Spaniard, aged 29, who was said to have had malaria 13 years before. One week before entry, he began to complain of abdominal pain and diarrhœa. Four days before entry, there was headache, anorexia and nausea.

On Oct. 12, 1909, he was admitted at about 2 p. m. with a temperature of 105.8° F.; pulse, 104; respiration, 24. His appearance was typhoidal; the spleen was large, soft and palpable; there were several suggestive rose spots. The blood showed no parasites. The count was:

R. B. C.	5,280,000
W. B. C.	5,600
Hæmoglobin	90%

The coagulation time was three minutes, thirty seconds.

Urine: Normal color; sp. gr., 1.015, slight trace of albumen. In other respects, not remarkable.

On Oct. 13, 1909, I saw the patient on a morning visit. The temperature had fallen from nearly 106° to 99.4° F. He had a characteristically typhoidal appearance. The temperature was regarded as suggestive of malaria, but fresh and stained specimens of blood were negative. The Widal test was negative; the Diazo reaction was positive.

The chart illustrates the course of events. Daily blood examinations revealed no parasites. There was a leucopenia of 3,800 to 5,200. Five days later, a slight jaundiced tint was noted. The blood pressure, which at the outset ranged from 97-114, was on the 19th, 84 mm. Hg.

I next saw the patient on Oct. 20, 1909, just a week after my first visit. At that time, the temperature was about 105° F. There was a great change in the general picture. The facies was very dull and typhoidal. There was a very distinct anæmia and a slight greenish-yellow jaundice. The respirations were from 28 to 30. The liver was readily palpable. The appearance was wholly characteristic of malaria. A fresh specimen of blood was taken immediately and a considerable number of æstivo-autumnal parasites were found. These were for the most part bodies containing

* Einführung in das Studium der Malariakrankheiten, 2 aufl. 8°, Jena, 1906, Fischer, 221.

a few fine pigment granules, often arranged as a central mass, sometimes in a block (pre-segmenting bodies). The patient was obviously an ill man. It was suggested that he be given vigorous treatment, i. e., quinine bi-muriate gr. xv (1 gm.) in 10 cc. normal salt solution intravenously, to be repeated, if necessary, in four hours, and afterwards, quinine sulphate gr. v (0.325 gm.) every four hours by mouth.

The solution was not made by the apothecary until several hours after the visit and then, by a misunderstanding, of double strength, so that at 12 o'clock on the 20th, the patient was given quinine bi-muriate gr. xv (1 gm.) in 5 cc. of normal salt solution. Immediately after its introduction, there was a momentary convulsion accompanied by a slight twitching of the eyelids and lower lip, followed at once by general spasmodic contractions of the trunk and extremities. The eyes were rolled up and the head was somewhat retracted and turned to the right. Recovery was almost instantaneous and the patient soon seemed better than he was before. Thereafter, he was given quinine sulphate gr. x (0.6 gm.) by the mouth, every four hours.

Oct. 21. At 1 a. m. the patient was given a second intravenous injection of quinine bi-muriate gr. xv (1 gm.) without unpleasant results. In the morning, the temperature had fallen to 100° F., the pulse was from 90 to 100, and the patient seemed better. At 4 p. m., however, the temperature was rising again and a third intravenous injection of quinine bi-muriate gr. xv (1. gm.) was administered. Immediately upon its introduction the patient began to show convulsive twitching of the eyelids and lips; this was followed by a general convulsion. There was marked cyonosis; the pulse disappeared; the patient failed to respond to stimulants or artificial respiration.

Re-examination of the stained specimen of blood made on the 19th, showed, after long search, two characteristic æstivo-autumnal rings, which had been overlooked on a previous examination.

The *necropsy* made by Dr. Thomas twenty-eight hours after death, showed a severe but not intense malarial infection. The brain showed nothing remarkable—little pigment in the vessels. The spleen was large and soft, and microscopically showed much pigment—for the most part in leucocytes. Smears showed numerous segmenting parasites. The liver weighed 2700 grammes and was of a slate color; the cut surface was opaque. There was marked parenchymatous degeneration and the capillaries contained much pigment. The bone marrow showed numerous parasites in smears.

Both kidneys showed marked cystic degeneration,—the right measuring 16 x 10 x 7 cm. The entire surface was studded with cysts, the diameter of which ranged from a millimetre or less to 2½cm. The contents varied in color—clear—brownish—opalescent, and in some instances apparently contained changed blood. The pelves were greatly dilated. On section, the tissue which remained showed few changes in gross, but microscopically, there was a definite increase in fibrous tissue and some congestion of the vasa recta; in the portion of the kidney showing cystic change, there was considerable cloudy swelling with marked increase in fibrous tissue. The cysts were lined with cuboidal epithelium.

This case is exceedingly interesting as an example of grave infection with few parasites in the peripheral circulation throughout a week of study and observation.

The occasional absence of parasites in the peripheral circulation, especially in grave cerebral cases, has been emphasized by many observers, notably by Bastianelli. I have never seen, however, a case of such severity with so long an absence of parasites.*

The correct diagnosis was suggested here by the character of the fever, the general appearance of the patient and the leucopenia, and, even in the absence of parasites, I should have ordered quinine when I saw him on the 20th.

The most interesting point in connection with the case is the question as to the cause of death. From the result of the necropsy and from my observation of the patient, I should feel sure that it was *not* due directly to his malarial infection; on the other hand, I should feel reasonably sure from the history of the case that it *was* directly due to the intravenous injection of the quinine.

The literature upon quinine poisoning is very large and there are many instances of apparent death from large doses. The amount administered to this patient was, however, by no means remarkable, although considerably larger than that which is customary in this hospital. Several points are, however, worthy of note.

The first of these is the concentration of the dose. The speaker has always been in the habit of giving quinine intravenously according to the method of Bacelli in a solution consisting of

	gm.
Quin. dihychlor.	1.
Aquæ	10.
Sod. chloridi	0.065,

one-half of this being given in one median basilic vein and one-half in the other. In this instance, a dose of double the concentration was given at once. The patient had received 6 grammes of quinine in 24 hours, 7 in 28 hours, 3 grammes having been administered intravenously. The direct sequence of the symptoms in connection with the first and third injections of quinine was such as to leave little doubt as to the relation of the dose to the manifestations. While the dose was certainly strikingly concentrated, yet one must probably assume also that the individual was hyper-susceptible to the drug.

The specimen of quinine was from the same sample which had been used in other cases, and, so far as could be made out, showed no impurity.

A point of interest in connection with the case which may have an important bearing upon the fatal outcome, is the fact that the patient had cystic disease of his kidneys. Prof. Abel was much impressed by this fact, feeling that it suggested strongly that an unusual retention of the drug might have contributed toward rendering the patient more susceptible to the last dose. It must be said that the excretory powers of the kidneys seemed to be good and that anatomically, there was still considerable cortical substance. However this may be, the observation seems to be worth recording. I have for years been in the habit of advising the intravenous injection of quinine in urgent cases. Such an experience as this would certainly suggest caution in administering a solution of a concentration greater than 10 per cent. More than this, it points, it seems to me, to the advisability of conservatism in the administration of quinine intravenously in other than urgent cases of pernicious malaria.

In conclusion, let me emphasize one point, an old lesson, after all, which these two latter cases illustrate, i. e., that while careful and repeated examinations of blood in a vast majority of cases answer the question as to the presence or absence of malarial infection, really grave malaria may exist for considerable periods of time without demonstrable parasites or pigment in the peripheral circulation. In case of doubt, do not delay too long before applying the therapeutic test.

* Although I did not examine these daily specimens, seeing the patient but twice, yet I am sure of the care with which the case was followed by a most capable ward physician.

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THE PREPARATION OF ANTITOXIN.*

By E. J. Banzhaf, Ph. D.,

(Research Laboratory, New York City Board of Health.)

I accepted the invitation of your secretary, Dr. Moss, to speak to this well-known medical society, of the Johns Hopkins Hospital, upon the subject of antitoxin, with a mixed feeling of pleasure and trepidation. With pleasure at the honor bestowed upon me, through your secretary, and with trepidation that I might not fulfill your expectations. Inasmuch as the protective and curative value of the antitoxins is well established, the chemistry of these antibodies is possibly not so attractive as researches on the more baffling diseases. However, any knowledge we can gain from the chemistry of the antibodies will help to solve other difficulties in general biology, physiology and pathology.

It is now about fifteen years since diphtheria antitoxin was introduced for the treatment of diphtheria. Hopes were entertained that the antitoxin would be isolated and purified. Up to the present time these hopes have been only partly fulfilled.

As early as 1893, Brieger and Ehrlich attempted to isolate the antitoxin from the milk of immune animals. Smirnow, in 1895, was probably the first to work with antitoxic horse serum. He showed that the active substance was precipitated with the globulins on saturating the serum with magnesium sulphate.

Brieger and Boer, in 1896, precipitated the globulins by adding neutral salts of the heavy metals and found the antitoxin in that protein. Aronson, in 1897, stated that the globulin precipitated by dialysis contained antitoxin.

Dieudonné showed that the globulins precipitated by carbon dioxide did not contain antitoxin.

The protein precipitate, obtained by both these workers, corresponded to the globulins of the serum as originally defined. This globulin is now known as euglobulin. Brodi, in 1897, separated the globulins into four fractions, by the progressive addition of ammonium sulphate to one half saturation. All four fractions contained, however, relatively equal amounts of antitoxin. Belfanti and Carbona, Freund and Sternburg, Marcus, Seng, Hiss, Atkinson and others confirmed the results of Brodi and Dieudonné.

Atkinson, in 1900, working in the Research Laboratory, saturated with sodium chloride a solution of globulins containing the antitoxin. By employing heat, he differentiated the globulins into several fractions containing antitoxin. The antitoxin corresponded to the quantities of globulin in the precipitates.

Pick, in 1901, attempted to differentiate the active portion of the serum by fractional precipitation with ammonium sulphate.

Pröscher attempted to isolate and establish the non-protein nature of antitoxin by digesting the serum with trypsin. He stated that in this way he obtained a solution containing antitoxin which was free from protein.

Mellanby and I, working independently in 1908, could not confirm Pröcher's work. The ratio of digestion of the protein was approximately the rate at which the antitoxin was destroyed.

That the antitoxins belong to that class of substances known as proteins, practically all investigators now agree.

It might be well, at this point, to call your attention to the fact that, in the early days, the antitoxic serum contained less than 100 units per cubic centimeter. This low grade of serum was principally due to the inability to produce a strong diphtheria toxin. Park and Williams, in 1896, isolated a diphtheria culture from a child with a mild case of diphtheria. This culture proved to be a strong toxin producer and is now used and known throughout the world as "Culture No. 8." With the toxin from this culture a more potent antitoxin was gradually obtained. Thus smaller injections of serum were required to give the same number of units. This was desirable, for it was early recognized, by Pirquet and Schick, that injections of antitoxic sera were sometimes followed, after an incubation period of eight to thirteen days, by urticarial eruptions, joint pains, fever, swelling of the lymph nodes, edema and albuminuria. These disturbances have no direct bearing on the antitoxic properties of the serum, for they showed that normal horse serum produces the same effects. This reaction Pirquet and Schick have termed "Serum Sickness."

Although almost all the investigators mentioned, and others, established the fact that the antitoxins were associated with the globulins, there was practically no record of actual administration of these globulins. Park, in 1900, first studied the possibility of eliminating serum rashes and other disturbances, by testing a considerable number of cases with an antitoxic globulin prepared by Atkinson. The results were practically identical with an equal number of cases treated with the whole serum from the same horse.

In 1905, Gibson, working in the Research Laboratory, perfected a practical method of recovering the pseudoglobulin containing the antitoxin. He placed the precipitated globulins obtained by half saturating with ammonium sulphate, in saturated sodium chloride solution. In this way the globulin, insoluble in saturated sodium chloride solution, *i. e.*, euglobulin, present in Atkinson's preparation, was eliminated. The pseudoglobulin, which is insoluble in the saturated sodium chloride, was precipitated with acetic acid. This precipitate was then dialyzed. The finished concentrated product was about two and a half times the original potency.

With this product, Dr. Park again took up the study of rashes. The results of this work were favorable. Less early

* Read before the Johns Hopkins Medical Society, December 19, 1910.

rashes, and constitutional disturbances, were noted. This preparation was so satisfactory, that the New York Board of Health laboratory in 1906 sent out only this product. Other laboratories then followed suit.

At Dr. Park's suggestion, Gibson and I fractioned the antitoxic serum with progressive amounts of ammonium sulphate up to one-half saturation. Our experiments resulted somewhat differently from those reported by Brodi, Atkinson and Pick. We found that the pseudoglobulin of the higher fractions contained uniformly much more antitoxin, per gram protein, than that precipitated by lower concentrations of ammonium sulphate.

Both from a theoretical and practical view, the results were very satisfactory. This fractioning of the antitoxic sera was adopted in preference to Gibson's original method.

After the partially purified antitoxin product was well established, the question occasionally arose regarding its protective and curative value in comparison with that of the whole serum from which it was derived. According to certain French investigators and others, the antitoxic serum most active therapeutically is not always the one which contains the greatest number of antitoxic units. They maintain that the serum contains, besides antitoxin, other important protective and curative substances, which are not measured by the present method of standardization. For instance, they state that a given quantity of a 200-unit serum is occasionally more active, both preventively and curatively, than the same quantity of a 500-unit serum. Roux, Marfan, Martin, Momont, Cruveilhier, and lately Kraus and Schwoner, support the French views, while on the other hand, some of the German, English and American investigators support Ehrlich's method of standardization.

The conclusions of the work of Steinhardt and myself, in which we used several strains of a 24-hour agar culture of live diphtheria bacilli, with antitoxic serum of widely varying strengths, were that, with diphtheria in the guinea-pig, the therapeutic value of the serum depended upon the number of antitoxic units present. No other substance, besides the antitoxin, played an important rôle. The conclusions of our work on the concentrated globulin containing the antitoxin, and the whole serum from which it was derived, were the same as just given. Since our work, in 1908, Kraus and Schwoner have published four papers on this subject. The conclusions of all of these are diametrically opposed to our findings. Berghaus, working in Ehrlich's laboratory, corroborated our findings, and stated that he found great discrepancies in Kraus' standardization of the antitoxic value of the serum.

I might state that we obtained three different samples of the horse serum that Kraus and Schwoner used in their work. These were labelled to contain 200, 350 and 600 units, respectively.

In my standardizations, I found the first to contain 185 units. Deterioration in transit might account for this difference. The sample said to contain 350 units actually contained 465 units. The 600-unit sample contained only 360 units. In regard to the accuracy of their standardization on the two latter samples, no comment is necessary.

We will now discuss briefly the work by Gibson and myself, on the quantitative changes in the proteins in serum of horses in the course of immunization.

Seng, Joachim, Atkinson and Ledingham observed that when an animal is immunized against bacterial toxins, there result certain characteristic quantitative changes in the proteins of the blood plasma. The content of the globulins is strikingly increased even up to double the normal amount; at the same time, there is a diminution in the albumin.

Atkinson showed that this globulin increase is in some degree proportional to the antitoxic potency of the serum.

Ledingham, in a paper published while our work was under way, gave results of the determination of the total protein, the globulins and the albumin in the course of immunization against diphtheria toxin. The serum was obtained at short intervals from two horses.

In one horse, which failed to yield a high grade of antitoxin, the globulins of the serum were not essentially increased over the normal. The other horse gave ultimately a 650-unit serum; the globulins here had progressively increased along with the antitoxic potency. From Ledingham's results from the two horses, a relation between the development of the antitoxic properties and the increase in the globulins is indicated. Ledingham and Joachim state that the increase of the globulins is in the euglobulin fraction.

It may be desirable to discuss the fractioning of the globulins. The globulins are commonly stated to consist of at least two different proteins, the euglobulin, and a more soluble protein, the pseudoglobulin. The euglobulin is insoluble in pure water, and accordingly precipitated on dilution or dialysis; it is also thrown down by slight acidification. The pseudoglobulin belongs by definition to the group of true albumins; *i. e.,* it is soluble in pure water. In practice, investigators have commonly used the fractional precipitation by salting out with ammonium sulphate. A half volume of saturated ammonium sulphate solution is added to the serum; *i. e.,* one-third saturation. The precipitate is the euglobulin. The separation is not sharp at all. The filtrate contains the albumin and pseudoglobulin; the latter can be thrown down by the further addition of saturated ammonium sulphate solution to half saturation. In current writings the identity of this "fractioned" euglobulin has been confused with the slight precipitate obtained on dialysis, dilution, or slight acidification, in spite of the early work of Freund and Joachim. By employing the ammonium sulphate fractioning, Ledingham, like Joachim, found the increase in the globulins affected the euglobulin more than the pseudoglobulin fraction, *i. e.,* the great increase in the globulins took place in the non-antitoxic protein. Ledingham's interpretation of his results, as regards this point, seems inconclusive, for he does not grasp the significance of the limitations in the salt fractioning of the proteins. His observations, associating the increase in the globulins with the questionable euglobulin fraction, were made by direct precipitation of the serum with half its volume of satu-

rated ammonium sulphate solution; *i. e.*, one-third saturation. When re-precipitated for purification, the protein was usually re-dissolved to the original volume and the same amount of ammonium sulphate solution added as before. Inasmuch as the globulins may have been doubled as the result of immunization, would not a great part of this increase be found naturally in the euglobulin fraction, since solubility of the protein must be considered? The precipitate obtained at one-third saturation is not free from antitoxin. It may contain the greater part of it when the undiluted serum is precipitated by the addition of a half volume of saturated ammonium sulphate solution. To illustrate this, Gibson and I precipitated ten cubic centimeters of plasma by the direct addition of five cubic centimeters of saturated ammonium sulphate solution; again, ten cubic centimeters of the plasma were diluted to $33\frac{1}{3}$ cubic centimeters with water and precipitated by the addition of $16\frac{2}{3}$ cubic centimeters of the saturated ammonium sulphate solution, and finally, a third ten cubic centimeters of the plasma were diluted to $66\frac{2}{3}$ cubic centimeters with water and precipitated with $33\frac{1}{3}$ cubic centimeters of the saturated ammonium sulphate solution. We then had ultimate dilutions of 15, 50 and 100 cubic centimeters each, at one-third saturation. The precipitates were allowed to stand for a few hours, with occasional shaking, to permit mechanically precipitated protein to return into solution. The precipitates, at the three dilutions, were then determined. We found the fraction to include 5.39, 1.78 and 0.98 grams of protein per 100 cubic centimeters at the three respective dilutions.

Because of this unsatisfactory characterization of the "eu-" and "pseudo-" globulin by the ammonium sulphate fractioning, it seemed of interest to differentiate in some modified way the relative globulin changes. We have accordingly determined as euglobulin that part of the globulins precipitated on saturating with sodium chloride.

Freund and Joachim state that saturation with sodium chloride precipitates all the euglobulin, but that this includes only a part of the product obtained at one-third saturation ammonium sulphate. We may consider that we have as sharp a differentiation as possible between the two globulins. The sodium chloride separation, probably, more truly represents the common conception of the euglobulin and pseudoglobulin, though the ammonium sulphate fractioning, heretofore, has usually been employed. With your permission, then, we shall term the globulin soluble in saturated sodium chloride solution, pseudoglobulin; and the globulin insoluble in saturated sodium chloride solution, euglobulin.

The observations of Atkinson and Ledingham were the only determinations of a quantitative relation of the globulins and the antitoxic potency throughout the course of immunization.

The subject is of extreme importance when the significance of the problem as to the chemical nature of the protective substances is considered, because of the constant relation of these substances with the pseudoglobulin, *i. e.*, the globulin soluble in saturated sodium chloride solution. In our work we followed quantitatively the protein changes in the plasma of eleven horses. The characteristic globulin increase during immunization was observed in all the horses. The increase was found in the pseudoglobulin.

We allowed about six weeks to elapse after the immunization was started, before taking a sample bleeding for analysis. From this time on samples were taken every week during the treatment. This first estimation gave us in all the horses an increase in the pseudoglobulin varying from 45 to 120 per cent, and a loss of albumin from 25 to 85 per cent. Thus it can be seen that great protein changes had taken place after only six weeks immunization. That we missed the time of early changes we realized after it was too late.

The total proteins showed an increase of from 20 to 45 per cent. This increase was at its highest after about two months of treatment and was true in all the horses regardless of unit content. After two and a half to three months treatment the total proteins decreased and fluctuated somewhat throughout their entire immunization.

The proteins, however, never dropped to the normal amount even though weekly full bleedings were taken; in some cases extending over a period of many months. This, therefore, shows us that the influence of repeated bleedings does not essentially influence the protein changes induced by immunization. These remarkable regenerative processes are worthy of note.

The highest antitoxic value obtained from these horses was 850 units; at this time the albumin was 75 per cent lower than this horse's normal amount, and the pseudoglobulin 90 per cent higher. An exceptionally refractory horse, with its highest value 125 units, showed a decrease of 55 per cent albumin, and an increase of 85 per cent of pseudoglobulin. Thus it can be seen that the decrease of albumin and the increase of pseudoglobulin take place in an immunized horse regardless of the antitoxic content. We wish to state, however, that the maximum antitoxic potency does not necessarily mean that other immune substances are present in greatest amounts or that they are developed in corresponding degree with the antitoxin. Immunization aimed to be of specific character may lead to the production of other antibodies. Collins and others have shown that group and specific bacterial agglutinins can be developed by immunizations against yeasts, enzyme preparations and nucleins.

These experiments afford actual proof of the development of many widely different anti-substances during immunization. A similar stimulation, leading to the formation of numerous antibodies besides the precipitins and specific antitoxins, probably occurs on immunization with bacterial toxins. Such substances may represent the increase in the pseudoglobulin with which they are associated.

In the course of immunization, then, there is a marked increase (even over 100 per cent) in the pseudoglobulin content of the blood plasma. This increase tends to precede the development of maximum antitoxic potency and is quantitatively independent of the latter. With a diminution of the potency, the pseudoglobulin increase is reduced, with a tendency for this change to precede the antitoxin variation.

This work on the protein changes brought out the fact that the proteins eliminated in the process of purification were much less than we had expected. For, as is well known, in the average normal horse serum the proteins are distributed as follows: albumin 40 per cent; pseudoglobulin 42 per cent; euglobulin 18 per cent. Thus it would appear that about 58 per cent of the protein was eliminated in the purifying process. We now know, however, that in the average immunized horse the proteins of the serum are distributed as follows: albumin 12 per cent; pseudoglobulin, containing the antitoxin, 78 per cent; euglobulin 10 per cent.

Thus only 15 to 25 per cent of the protein could be eliminated, depending on the fluctuation of albumin and euglobulin content of immunized horses.

Early in the spring of 1908, an observation of Stark's came to my notice.

Stark showed that when egg albumen was heated for one hour at 56° C. a portion of it was converted into a body, which appeared to be a globulin because of its precipitation and solution reactions. This fact aroused my curiosity as to what result would be obtained if antitoxic serum or the antitoxic pseudoglobulin solution was heated. With this in view, I carried out a large series of heating experiments with results that were rather gratifying as a means of further purifying the antitoxin. This gave at least 50 per cent purer antitoxin than had ever before been obtained. In order to make this clear, we will take the serum of an immunized horse. The proteins of this animal's serum, we will assume, are distributed as follows: albumin 12 per cent; pseudoglobulin, containing the antitoxin, 78 per cent; euglobulin 10 per cent. If we heat this serum from twelve to fifteen hours at a temperature of 57° C. we will have a rearrangement of the precipitation characterization of the proteins. If we now estimate the albumin, we will find, instead of 12 per cent, only about 9 per cent; the pseudoglobulin, containing the antitoxin, instead of 78 per cent, only about 50 per cent; and the euglobulin, instead of 10 per cent, will be increased to about 41 per cent. All of the antitoxin, with the exception of about 7 per cent which is lost by the heat employed, will be found in the remaining pseudoglobulin.

From a scientific standpoint, this is extremely interesting, in that it opens a new field for further investigation, which may throw more light on the chemical characteristics and the nature of antitoxin.

Formerly, all the evidence was in favor of the pseudoglobulin nature of the antitoxins. The antitoxins had every known character of this protein. Mellanby, in 1908, stated that antitoxin is actually a part of the pseudoglobulin. Now, however, we know that we can heat the pseudoglobulin, containing the antitoxin, and actually change the precipitation limits of about one-third of it, *i. e.*, from the pseudoglobulin to the euglobulin condition, without loss of antitoxin. From this we can conclude that the pseudoglobulin in an immunized horse is not necessarily antitoxin. The chemical combination of pseudoglobulin and antitoxin, if such is the case, is not a fast and stable one. If a union does exist it must be merely an unstable combination that can be disassociated by heat. As an analogy to this, Calmette's work on cobra venom and its antitoxin might be mentioned. Calmette, you will remember, showed that when neutral mixtures of venom and antitoxin were heated, the antitoxin lost its identity and the venom regained its toxicity. He stated that the mixture of venom and antitoxin form an unstable combination and that each of the two substances preserves its individuality in the mixture.

From the knowledge we now have in regard to antitoxin, it is justifiable to conclude that there is a union between the antitoxin and pseudoglobulin, either a mere adsorption or an unstable chemical combination, and that the antitoxin can be disassociated from the pseudoglobulin without losing its identity.

THE CLINICAL VALUE OF THE DETERMINATION OF THE CATALYTIC ACTIVITY OF THE BLOOD.

By M. C. Winternitz, M. D.,
Associate in Pathology in the Johns Hopkins University.

(*From the Pathological and Medical Clinical Laboratories of the Johns Hopkins Hospital.*)

Catalase is an enzyme of universal occurrence characterized by its power of decomposing hydrogen peroxide with the liberation of water and molecular oxygen. Further than this very little is known concerning its function. Its intimate occurrence with peroxidase, however, has led to the assumption that these two ferments are associated in the oxidative phenomena of the body.

The following report is based upon a series of experimental and clinical investigations in which C. R. Meloy, G. R. Henry, F. McPhedran, J. P. Pratt, and W. B. Rogers were associated with the author.

Experimental Work.

The study of the catalytic activity of both normal and diseased human tissues and of the blood in experimentally produced diseases in animals is confined to a few isolated observations. For this reason we have first interested ourselves in this field and the results of these investigations seem so essential for the proper interpretation of the clinical application of the test that they will be briefly summarized.

The determination of the catalytic activity of human tissues led to the conclusion that all of the tissues of the body were reduced in their power to split hydrogen peroxide in chronic

nephritis, and that this reduction varied directly with the severity of the condition. The lowest activity was obtained in uræmia. In no other disease, including eclampsia, was this universal decrease in the activity of the enzyme found (1).

After it had been determined that the catalytic activity of a single rabbit's blood is constant from day to day over long periods of time the influence of the kidney and its function upon the catalase of the blood was studied with the following results: after ligation of the ureters, bilateral nephrectomy or uræmia, resulting from uranium nitrate nephritis there is a fall in the catalytic activity of the blood which becomes more and more evident as death is approached. The tissues of such animals at autopsy show a like reduction (2).

The effect of salts on the catalytic activity of the blood of living rabbits was then investigated for the following reasons, (1) because it is well known that the addition of various salts to a catalase extract in vitro influences the action of the enzyme, and (2) because the decreased activity of the catalase of the blood in nephritis might in some way be related to the salt retention in this disease. The results seem conclusive. Acids, alkalies and salts all reduced the activity when injected intravenously. In these experiments it is important to make observations during the injection and at short intervals after the injection has been discontinued, since there is a rapid compensation on the part of the organism with a return to normal of the catalytic activity of the blood. For example, 20 cc. of 5 per cent bicarbonate of soda solution causes a marked fall in the activity of the blood which is rapidly recovered from (1 to 5 minutes after the injection has been discontinued) and then a much more marked fall in the activity followed by a much longer time for compensation occurs after 6 cc. of the same salt. This continues on further injections until compensation is lost and death ensues. It is possible on this basis to construct a hypothetical explanation for the decline of the catalase in nephritis and uræmia (3).

Further studies on the relation of various organs to the catalytic activity of the blood were made with these results. After the extirpation of many organs there is a transient fall in the catalytic activity of the blood. The fall is permanent after extirpation of the thyroid, but is compensated if thyroid be fed (4).

During the above experiments it was found that following an acute peritonitis there may be a sharp rise in the catalytic activity of the blood. This rise usually occurs within 6 hours after the peritonitis is produced, and may continue for several days. The curve of activity is entirely independent of that of the body temperature or white blood count, but corresponds to an increased number of erythrocytes (5 and 6).

From the above experiments several factors influencing the catalytic activity of the blood can be deduced, namely the number of red blood cells, the function of the thyroid and kidney, and the action of salts, acids, and alkalies.

Clinical Application of the Test (7).

Method.—.025 cc. of blood is removed from the lobe of the ear in a pipette. This is diluted in 10 cc. of water; 5 cc. of this dilution suffices for a test. It is placed in a 100 cc. bottle in which there is also a vial with 5 cc. of neutral hydrogen peroxide. The large bottle is connected with a gas burette and then uniformly agitated in order to bring the blood and hydrogen peroxide in contact. The amount of oxygen liberated is measured over a given period of time (15 seconds). The procedure requires only a few minutes, the error is slight and no precautions beyond ordinary room temperature and clean apparatus are necessary.

A series of 100 normal individuals of different age and sex were first studied; 80 per cent of these vary within physiological limits, i. e., 5 cc. of a 1-400 dilution of their blood will liberate from 13 to 17 cc. of oxygen from 5 cc. of neutralized 3 per cent hydrogen peroxide in 15 seconds. In the other 20 per cent the amount of oxygen liberated varies within wide limits, 12-22 cc. These variations are independent of the number of red blood cells and hemoglobin percentage. The explanation of this variation is at present not forthcoming. It is, however, of the utmost importance to bear it in mind when interpreting the activity of the blood in diseased conditions.

On the other hand the catalytic activity of the blood of a single normal individual is constant from day to day over long periods of time and in this way a base line can be obtained from which the significance of any change in the activity can be readily interpreted.

The Catalytic Activity of the Blood in Disease.

Typhoid Fever.—Fifteen cases were followed throughout their illness with the following results. During the early days of their illness there was no change in the catalytic activity of the blood, but towards the third week there was a gradual fall accompanying the anemia. During convalescence the activity became normal together with the red blood count.

Diseases of the Respiratory Tract including lobar pneumonia, tuberculosis, and empyema (12 cases). There is a slight decline in the catalytic activity of the blood during the course of lobar pneumonia. The relation of this decline to the crisis and the salt metabolism of this disease has not yet been determined. In other diseases of the respiratory tract there is no noteworthy variation in the power of the blood to split hydrogen peroxide except where the disease is accompanied by a severe anemia.

Acute Peritonitis.—In 4 out of 5 cases of acute peritonitis examined there was a characteristic rise in the catalytic activity of the blood. In one a reading had been made before the peritonitis occurred while in the other three the increased activity was confirmed by the decline to normal, following operation. In the one instance where no rise was obtained the reading was only made 20 hours after operation. In two cases of suspected peritonitis with high fever and leucocytosis the catalytic activity of the blood was normal, and in these cases the peritoneum was found clean at operation.

Diabetes Mellitus and Catarrhal Jaundice exert no influence upon the catalytic activity of the blood.

Diseases of the Thyroid Gland.—Four cases. In diseases of the thyroid gland both hypo- and hyperthyreosis, the catalytic activity of a single patient's blood is not constant from day to day. In hyperthyreosis the activity tends to increase while in hypothyreosis the activity assumes a level lower than normal. This may be of significance in interpreting the condition of the thyroid gland where the signs and symptoms are atypical.

Renal, Cardiac and Cardio-Renal Cases.—Twenty-four cases.

1. Despite the presence of a marked nephritis provided there are no symptoms of renal insufficiency (uræmia) there will be no marked change in the catalytic activity of the blood.

2. Where there is a chronic nephritis accompanied by indefinite symptoms of renal insufficiency the catalytic activity of the blood will be irregular from day to day and will tend to assume a level lower than normal.

3. In acute mercurial nephritis there is a fall in the catalytic activity of the blood.

4. With uræmic coma there is a marked fall in the catalytic activity of the blood which is permanent if the coma ends fatally but which recovers should the coma disappear.

5. With retention of urine due to obstruction of the lower urinary tract there is a marked decline in the catalytic activity of the blood. This decline may persist for some time but should the obstruction be removed the catalase will again rise.

Cardiac Cases.—Even in severe cardiac disease there is no significant change in the catalytic activity of the blood. In some cases it is high. This may be normal for these individuals as it will be remembered some normal individuals have a high activity. In no single case was the activity sufficiently decreased after many readings had been made to suggest renal insufficiency.

Cardio-renal Cases.—In three cases of cardio-renal disease where the clinical findings suggested a renal insufficiency the catalytic activity of the blood was normal. At autopsy only a chronic passive congestion of the kidneys, the result of a decompensated heart, was found.

Cerebral Hemorrhage.—In two cases of cerebral hemorrhage the catalytic activity of the blood was high. Whether this is an increase over normal is not known but it is clear that the high reading would differentiate apoplectic coma from uræmic coma.

The Catalytic Activity of the Blood in Pregnancy.

Neither pregnancy nor labor have any appreciable effect upon the catalytic activity of the blood. Ten cases.

The toxæmias of pregnancies accompanied by coma and convulsions can be differentiated into two groups by the determination of the catalytic activity of the blood.

1. Cases where there is no change in the catalytic activity. These will include eclampsia without renal involvement. Seven cases.

2. Cases with decreased catalytic activity; three cases. These will include:

a. Chronic nephritis where the excessive work thrown on the kidneys by the fœtus will bring about renal insufficiency.

b. Eclampsia, etc., with marked renal involvement. The significance of this differentiation in the prognosis for future pregnancies is clear. In the first group future pregnancy may be normal. In the second it will most likely be complicated by a toxæmia, the result of renal insufficiency.

Malignant Disease and Diseases of the Hæmatopoietic System.

The results are still too meagre to be of value.

The interpretation of the clinical results is entirely dependent upon the experimental work, and in many places will probably be unsatisfactory. The number of cases is likewise too few to allow of anything but broad conclusions. It seems, however, that the work will be of value in the study of the oxidative phenomena of the blood, in further detail than is allowed from the enumeration of the red blood cells and the determination of their hemoglobin content.

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DISTOMA PULMONALE IN WISCONSIN.

By Henry Hanson, M. D.

(From the Pathological Laboratory of the Milwaukee County Hospital.)

The finding of lung flukes (Distoma Pulmonale, or Paragonimus Westermanii) is of such rare occurrence and great importance that it seems to me the case in question should be reported. Up to the present time there appear to be only three specific cases in which this parasite has been found in domestic animals in this country. One case has been reported for man, an imported case seen in Portland, Oregon. In the March (1908) number of the *Denver Medical Times* and *Utah Medical Journal,* E. W. Lazell reported a case of "Cysticereus cellulosæ and Distomum pulmonalis in Brain, with Exhibition of Specimens." This paper deals so briefly with the case, and the description of the parasites is so incomplete that one can hardly feel satisfied to class them with the group of parasites known as the Paragonimus Westermanii, and yet the paragonimus is the only fluke which is known to get into the brain.

Up to the present time the disease has been unknown in the State of Wisconsin. The only two other States previously known to have these parasites are Michigan (Ann Arbor) and Ohio (Columbus and Cincinnati). In Ann Arbor the fluke was found in the lung of a cat and was sent to Dr. H. B. Ward of the University of Nebraska, who identified the parasite and wrote the first report of the presence of this lung fluke in the United States. The parasites were later sent to Stiles of the Department of Zoology, Public Health and Marine Hospital Service, U. S., who confirmed Ward's diagnosis and pronounced them identical with the Paragonimus Westermanii. In the second case the lung fluke was found in a dog in Columbus, Ohio, by Kellicott, who also referred this specimen to Ward. In the third instance the lung fluke was found in hogs slaughtered at the abattoirs in Cincinnati, Ohio. These cases cited, together with the finding of the disease in a cat and also two of her kittens (kittens born in the village of Wauwatosa, Wisconsin), add further proof of the endemic theory of the infection. This means that we have a new parasite to deal with. The reason this parasite has not been discovered before is most likely due to the fact that it has not been looked for extensively. There is no doubt in my mind that there are cases of this disease in human beings which have been overlooked simply because an infection of this kind has not been known to exist.

This parasite, as is well known to those who have had occasion to look up its history, is a particularly unwelcome one. It is especially important that medical men should be on the lookout for possible cases of this infection, parasitic hæmoptysis, which are probably called incipient tuberculosis on account of the obscurity of the physical lung findings. The scattered distribution of the cases referred to would also indicate that the parasite is quite firmly established and that it is more common than is generally known. The first finding of the parasite dates back to 1893, the first report by Ward to 1894. Other reports have appeared at intervals, to which references will be given at the end of this paper.

The present paper is especially concerned with the finding of lung flukes in two autopsied cats in Wauwatosa, Wisconsin.

I am indebted to Mr. Edwin Hirsch, of Wauwatosa, Wis., for the opportunity of making this study, since it is through his interest in the case that the parasite was discovered. He first noticed that one of the cats owned by the family was coughing and in order to determine the cause of the cough he killed and dissected the cat. Later when a second cat began to show symptoms it was brought up to the laboratory of the Milwaukee County Hospital where the cat was chloroformed and autopsied.

History of Cat.*

Case I.—The first case of lung flukes to come under our observation was that of a female cat. Early in the spring of 1906 she with three other kittens was found under an old lumber pile. The other kittens were taken away, but this one was kept and grew up as a family pet. After she had become somewhat more than a year old, we noticed that she had a very peculiar cough. This was not clear and free, but rather close and choking. We at first thought little of the matter and permitted the cat to remain a pet. The cough gradually grew worse and the cat seemed to lose weight. As we did not deem it well to have a sick cat as a pet we concluded to dispose of her. During the Christmas holidays of 1908 the cat was chloroformed and autopsied. The lungs at their apices were of normal color, but at their bases colored nodular areas were to be seen. Upon cutting into one of these areas we were greatly surprised to find two parasites contained therein. Upon opening the other cysts, for now it was evident that these dark colored nodules were such, other pairs of parasites were found. In all there must have been 6 or 8 different cysts and each contained two parasites.

Case II.—The second case of lung parasites was also in a female cat. The cat, a kitten of the cat in the first case, was born on March 25, 1908. When but a few months old she also gave indications of a throat or lung trouble by a choking cough. This gradually became more marked and the cat grew thin. Finally she had several hemorrhages and then she was chloroformed, and autopsied on Easter Sunday, 1909, in the Pathological Laboratory of the Milwaukee County Hospital.

Anatomical Findings.—With the exception of the lungs the findings were negative.

Lung of Cat.—The upper lobe of the lung is of salmon red color, crepitates and shows no infiltration except in the lower part where a few areas of induration can be seen which somewhat resemble tuberculosis nodules. The nodules vary in size. In the lower lobe there are more of these areas, some of which are from 1 to 2 mm. or more in diameter. These have a semitranslucent appearance, and are of an opaque grayish-white color. Other areas in the lower part of the lower lobe are of a dull dirty brownish-gray with a yellowish-green tinge in the underlying tissues. Along the mediastinal portion there are more of these grayish, dull, semitranslucent areas. In the lower part of the

* History written by Edwin Hirsch, Wauwatosa, Wis.

lower lobe one sees a projecting nodule and a more voluminous appearance in the lung. On section one cuts into a definite cyst which contains two lanceolate bodies somewhat coffee-bean shaped, but the blunter head end differs from the narrower tail end and thus to some extent destroys the analogy of the coffee-bean. The fluke resembles the larva of the potato bug (dorsal surface). The flukes each have a rounded dorsal and a flattened ventral surface.†

The flukes in this case measured 11 mm. long by 4 to 4.5 mm. wide and in the fresh live condition about the same in the dorso-ventral diameter. On inspection one can see dark, blackish-blue areas which, as I have found on further study, are the internal organs such as uterus and intestines. One of the flukes was cut accidentally and as a result secreted a dark biliary, viscid-looking fluid substance. Color of flukes, a reddish-brown. On section of the lung one finds a more or less infiltrated appearance, with nodules of varying size. The cut surface in such areas has a yellowish appearance and smears from these areas reveal a large number of eggs with a chitinous yellow shell. The smears are obtained by simply drawing a slide across the fresh lung surface. These eggs are oval, one end blunter than the other, the blunter end has a definite operculum. Within the eggs are found varying pictures. Some seem to be simply an empty shell while others have a definite yolk or nuclear structure in the center of the egg mass. The eggs with the yolk mass also contain some cells which have the appearance of endothelial cells, but have a very granular protoplasm, almost resembling the granules of the *Herzfehlerzellen*.

Microscopic Findings.—Section, stained with hæmotoxylin and eosin, taken through the fibrous cyst with some of the surrounding lung tissue. In the gross this shows a fibrous capsule about the parasites, about 1 mm. thick with a dense surrounding infiltrated tissue. Microscopically this is found to be composed of whorls of fibrous tissue with some round, spindle and fibroblastic cellular infiltration. The picture is that of a chronic inflammation resembling a fibrous pneumonia. In the center of this cyst there are some organizing blood clots and an accumulation of round cells, other leucocytic cells, and here and there an occasional egg. Outside of this cyst wall one sees a dense pneumonic infiltration, of endothelial, round and polymorphonuclear cells, also giant cells. Within the eggs one finds in many instances a nuclear cleavage, probably the beginning development of the egg. Such a theory has already been advanced by one writer and discredited by others. Nevertheless such is the picture which is found in the eggs in the sections from this case. The section also shows empty shells of eggs. The significance of this cannot be definitely stated. The eggs of other flukes are not known to develop and liberate their ciliated embryos in the tissues.

Among other flukes which occur and may be pathogenic for man are the following: Liver flukes (Fasciola hepatica, Fasciola gigantica), and the Venal Distoma (Schistosoma hæmatobium), the latter is also known as Bilharzin, the disease, Bilharziosis or Egyptian Hæmaturia. The Schistosoma is a very rare parasite in this country and not more than six or seven cases have been reported. The last of these reports which I have seen is "Parasites Found in New York City, Archives of Internal Medicine, September 15, 1908, Vol. 2, No. 2, by H. S. Patterson." Other flukes have also been reported, e. g., Ward in 1895 reported "The European Cat Fluke, Opisthorchis felineus," from cats in Nebraska. This fluke, however, infests the gall ducts of the domesticated cat, and is not found in the lungs.

Clinical Diagnosis.—Diagnosis of lung fluke infection can be made by examining unstained specimens of sputum from suspected cases. The finding of large, yellowish, oval eggs should at once make the diagnosis. There are no other eggs the size and shape of the lung fluke eggs which are likely to be found in the sputum. "The eggs are always present and constitute the only constant specific character." Stiles (Osler's Modern Medicine) estimates that as many as 12,000 eggs may be expectorated in a single day. The cough is at first a hard, dry, chronic cough. The sputum is said to have a peculiar odor, probably due to the blood which it contains, and is of a rusty color.

"The lethality has not been determined but probably varies with the intensity of the infection." (Stiles, *l. c.*)

The lesson to be drawn from finding this parasite in this vicinity and other parts of the country is that there may be

† For a detailed description of the parasite I will quote from Illustrated Key to the Trematode Parasites of Man. Bulletin, No. 17, Hygienic Laboratory, Treasury Department, Washington, D. C.

"Type Species Paragonimus Westermanii (Kerbert, 1878).

"The Asiatic Lung Fluke—Paragonimus Westermanii—(Kerbert, 1878)—Stiles & Hassall—1900 of Man.

"*Specific Diagnosis.*—Paragonimus: 8 to 16 mm. long (after Kellicott 15 to 20 mm.), 4 to 8 mm. broad, 2 to 5 mm. thick; plump pinkish to reddish-brown (alive), slate color when preserved; live specimens are depressed and with a variable outline; preserved specimens often oval to elongate pyriform, transverse section round or nearly so, anterior end bluntly rounded, posterior end less blunt. Oral sucker 0.53 to nearly 0.75 mm. (Leukart) or more; 0.864 by 1.017 mm. or 1 to 1.4 mm. (Ward); or 0.40 to 1.12 by 0.83 mm. (Stiles and Hassall); 0.78 mm. (Kerbert) in diameter, terminal or subterminal in different specimens from the same lung. Ventral acetabulum 0.6 to at most 0.75 mm. (Leuckart); 0.78 mm. (Kerbert); 0.75 to 1.017 mm. (Ward); 0.88 to 1.2 by 0.86 to 1.44 mm. (Stiles and Hassall) very slightly larger than oral sucker. Skin provided with broad scale-like spines. Pharynx elongate; esophagus very short so that the bifurcation of the intestines is considerably anterior of the ventral acetabulum; intestinal ceaca usually somewhat zigzag some distance from each other run irregularly to posterior end. Genital pore, often indistinct, close to caudal margin of ventral acetabulum, may be in the median line or immediately to right or left of it. Male organs: Cirrus or cirrus pouch absent; ductus ejaculatorius is straight; testicles tubular, ramified, one slightly posterior of the other on each side of the median line. Female organs: Ovary branched lateral, right or left of medial line, somewhat posterior of acetabulum and anteroventral of transverse vitello-duct; on the opposite side of median line and at about the same height is situated a lobate shell gland and a rather short massed uterus: in some specimens the latter may spread across the median line and partially cover the ovary; folds of uterus extend ventrally of shell gland; vitellaria marginal, highly developed, extending anterior to posterior extremity, often leaving but a small portion of the dorsal and ventral median fold uncovered; transverse vitello-ducts dorsal; vitelline reservoir large; Laurer's canal present. Eggs oval, 80 to 100 μ long by 56 μ broad (Leuckart); 96 to 118 μ long by 48 to 53 μ broad (Ward); 68 to 96 long by 48 to 60 μ broad (Stiles and Hassall); yellow shell. Miracidium ciliated, develops after eggs leave host. Sporocyst, redia, cercaria, and intermediate host undetermined.

"*Habitat.*—Lungs and brain (occasionally in other parts of the body), royal tiger (Felis tigris), domesticated cat (Felis catus domesticata), domesticated dog (Canis familiaris), swine (Sus scrofa domesticata) and man (Homo sapiens).

"*Geographic Distribution.*—China, Japan, Formosa, occasional imported cases in Europe, some cases of endemic infection in the United States."

more of them in persons suffering from vague pulmonary symptoms, and that the physicians should always be on the lookout for them, especially where the parasite is now positively known to exist. All efforts should be made to determine, if possible, the mode of infection. So far the secondary host for these lung parasites has not been determined. All the writers upon this subject discredit the theory of direct transmissibility from one animal to the other of the same species. It would be contrary to all analogy. In the cases in question, where the mother cat had the infection and both of her kittens later developed the infection, one can explain the transmission by the fact that the mother and kittens ate of the same food.

In connection with the discovery of this case, the query, are we in danger of the spread of the infection among human beings? is a pertinent one. What danger are we in from eating raw vegetables in infected districts? May not some of our obscure pulmonary cases which have been diagnosed as tuberculosis be, truly, lung fluke infection, especially where the symptoms are not severe and where one is unable to find the tubercle bacilli in the stained sputum.

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BLOOD PLATELETS AND MEGALOKARYOCYTES IN HODGKIN'S DISEASE.[1]

By C. H. Bunting, M. D.

(From the Pathological Laboratory of the University of Wisconsin.)

During the progress of a clinical and pathological study of Hodgkin's disease, which has been undertaken by the author in conjunction with Dr. J. L. Yates, of Milwaukee, certain features of the blood picture have been observed which seem worthy of note. They are of constant occurrence in the disease and appear characteristic of it. Before describing them it seems best to define the condition designated Hodgkin's disease so that there may be no confusion regarding the cases in the mind of the reader. The term is used in the sense of Reed, Longcope and Simmons to denote a non-tuberculous disease most common in young males (though by no means confined to them) characterized by a progressive enlargement of the lymph-glands, by a tendency to an anæmic state, by certain pressure symptoms and by a fatal termination, usually within a period of from three to five years. The lesion in the lymph-glands shows a progression from a hyperplastic cellular stage to a final condition of sclerosis. According to the terse and accurate description by Longcope[2] there is "an early increase in the lymphadenoid tissue with later proliferation of endothelioid cells, formation of uninuclear and multinuclear giant cells, thickening of the reticulum and a final overgrowth of connective tissue. Eosinophiles, though not specific, are frequently found in great abundance." To this might be added the fact that the architecture of the gland is early destroyed.

My first opportunity to study the blood of a Hodgkin's patient came at a time when I was engaged in an experimental study of the origin and of the relations of blood platelets and my attention was attracted by the remarkable platelet picture in the blood smears from the patient (Case I). The blood platelets of the smear were very well preserved and, stained by Wright's stain, showed the characteristic clear blue protoplasm with sharply cut border and with the central group of metachromatic purplish granules. The platelets were exceedingly numerous. In fact I could not recall having seen any blood smear in which the number of platelets equalled that seen in this. In addition to this increase in number there was a striking variation in their size and shape. Many were round and approached the size of a red blood corpuscle. Oval forms also were found, from 15 to 20 μ in length and from 7 to 10 μ in width. Others took the form of pseudopodia, of about 4 μ in width and from 20 to 30 μ in length. From the sharpness of outline of these forms and the arrangement of their granules there was no question of their being due to the fusion of platelets. The picture was entirely different.

At a subsequent visit from the patient, who had in the intervening four months been under treatment with the X-ray, the same striking picture was present in the blood smear, and a count of the platelets by the Pratt method showed their number to be 1,140,000 per cmm.

Since seeing this case I have had opportunity to examine blood smears from eight other cases and to count the platelets in two of them. It does not seem necessary to report the cases in detail at this time, as clinical reports of the majority of them will be made in a subsequent paper. In addition to

[1] Paper read before the Association of Pathologists and Bacteriologists, May 3, 1910.

[2] Bull. Ayer Clin. Lab., 1903, No. 1, p. 4.

FIG. 1.

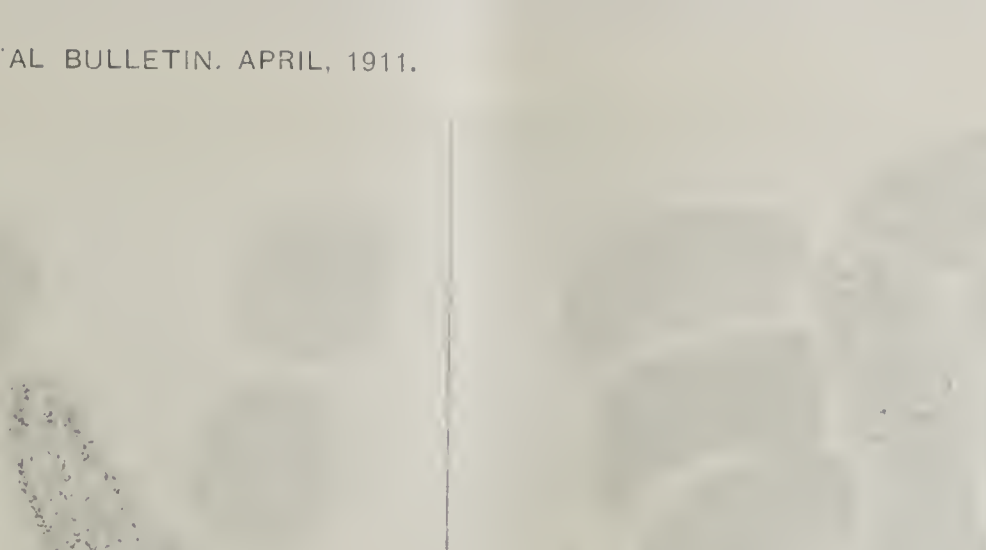

FIG. 2.

FIG. 3.

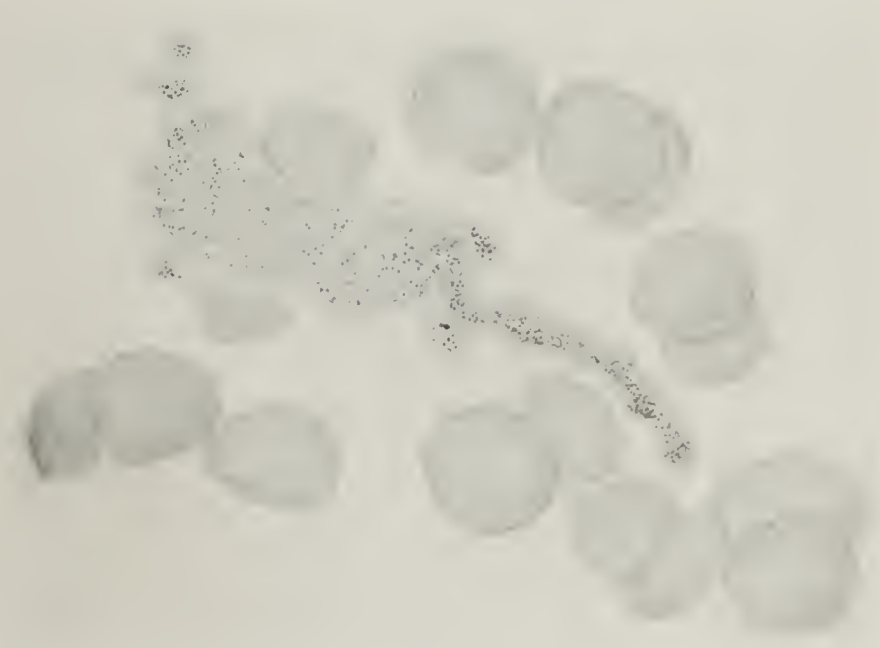

FIG. 4.

the brief outline of the cases here given it should be said that with one exception (Case VII) the clinical diagnosis of Hodgkin's disease has been confirmed by the examination of a gland removed for that purpose. The cases are briefly as follows:

Case I.—Nov. 20, '08 (Dr. Yates). Male, white, 21 yrs. Onset in July, '08. Cervical and axillary glands involved. Oct. 30, '08, gland removed for diagnosis showed early Hodgkin's changes.

Nov. 20-08. R. b. c., 5,304,000; w. b. c., 7500.
Mar. 4-09. R. b. c., 4,968,000; w. b. c., 4800; platelets, 1,140,000.
June 11-09. R. b. c., 5,600,000; w. b. c., 7000; platelets, 475,000.
Feb. 16-10. R. b. c., 5,800,000; w. b. c., 7000.

Case II.—Nov. 10, '08 (Dr. Yates). Male, white, 10 yrs. Large mass of discrete glands in left cervical region of at least one year's duration. Test gland showed well-marked Hodgkin's picture. Glands removed at operation Nov. 10, '08.

Apr. 1-09. R. b. c., 4,712,000; w. b. c., 9500; platelets, 750,000.
Jan. 22-10. R. b. c., 5,250,000; w. b. c., 9600.
Oct. 8-10. R. b. c., 4,960,000; w. b. c., 9800; Von Pirquet test neg.

Case III.—Apr. 1, '09. Male, white, 30 yrs. Seen two weeks after second operation for enlarged glands of neck. First operation six months previous at Rochester. Diagnosis Hodgkin's disease.

Apr. 1-09. R. b. c., 4,560,000; w. b. c., 10,000; platelets, 720,000.

Case IV.—Feb. 5, '10 (Dr. Tupper, Eau Claire, Wis.). Female, white, 40 yrs. Eight months previously right inguinal glands began to enlarge. Two months later left inguinal and left axillary glands; four months later, left cervical glands and one in right cervical region. Test gland showed advanced Hodkgin's lesion.

Case V.—Nov. 9, '09 (Dr. Yates). Male, white, 8 yrs. Swelling of cervical glands began five months ago; on date left inguinal glands also enlarged. Test gland showed early hyperplastic stage of lesion.

Nov. 9-09. W. b. c., 9900.
Jan. '10. Left cervical group of glands removed.
Feb. 26-10. R. b. c., 5,000,000; w. b. c., 5000.
Oct. 8-10. Von Pirquet test negative.

Case VI.—Mar. 10, '10 (Dr. Sullivan, Madison). Male, white, 16 yrs. Marked involvement of left cervical glands. Had been noted for only one month. Examination of test gland suggested greater duration, from the sclerosis and advanced condition of the lesion.

Mar. 10-10. W. b. c., 18,000.

Case VII.—Jan. 5, '10 (Dr. Bennet, Oregon, Wis.). Female, white, 64 yrs. Onset in inguinal glands, March, 1909.

Oct. 24-09. General glandular enlargement with clinical diagnosis of Hodgkin's disease.
Jan. 5-10. R. b. c., 3,200,000; w. b. c., 4450.
June 30-10. Death from exhaustion and anæmia.

Case VIII.—(Dr. Yates). Male, white, 33 yrs. Onset in March, '07 with supraclavicular glandular enlargement.

Sept., '08. Left supraclavicular and left axillary glands most enlarged. Some enlargement in right cervical, axillary and inguinal region.
Oct. 30-08. Excised gland shows typical and advanced Hodgkin's lesion.
Jan., '09. Blood smears examined.
May 20-09. Patient died.

Case IX.—Oct. 3, '10 (Dr. Yates). Male, white, 5 yrs. Left cervical glands markedly enlarged. Five months duration. Test gland shows marked Hodgkin's changes.

Oct. 3-10. R. b. c., 4,800,000; w. b. c., 4200.

In the two cases in which the platelet count was made (Cases II and III) the counts were as noted, 750,000 and 720,000 respectively, numbers which are well above the limits ordinarily given as normal. While three counts form a limited number on which to base a statement that the platelets are increased in Hodgkin's, I am relying also on the appearance of the stained smears from the six cases uncounted. Comparison of these six with blood smears from the three cases counted and with smears from normal individuals shows that in the Hodgkin's cases there is a definite increase in the platelets. There was no exception to this finding in the series. Furthermore, as constant as this finding, is that of platelets of unusual size and of the pseudopodia-like masses. These latter have varied much in size and shape, the longest approximating 50 μ in length. Their staining is identical with that of the platelets. The distribution of granules and the sharp borders preclude the possibility of their being fused platelets. Their general character can best be indicated by reference to the camera lucida drawings of a few specimens shown in Figures 1-4. My experience with these cases leads me to believe that these masses and pseudopodia are so frequent that one can scarcely fail to find them in any smear from an active case of Hodgkin's disease. On the other hand, in searching for them in the blood of normal individuals, I have found but one small pseudopodium in a careful examination of blood smears from fifteen individuals.

The question naturally arises: What is the nature of these masses which take the platelet stain? I have spoken of them as pseudopodia as I find they are identical in form and staining reactions with the specimens of Wright and with the figures published in his demonstration of the origin of platelets from the megalokaryocyte pseudopodia.[3] Further, as I have indicated in a previous paper,[4] I have been able to confirm Wright's findings in the rabbit and have found similar pseudopodial masses in the capillaries of the bone marrow and of the lung. I think it can be stated definitely, therefore, that these masses of platelet nature observed in cases of Hodgkin's disease are masses of megalokaryocyte protoplasm and of unconstricted pseudopodia of the same.

In an attempt to explain why these pseudopodia should be found in the peripheral blood stream in such numbers, while they are very infrequent in the peripheral blood of normal individuals, my attention was directed by previous experimental work to the lungs. Investigations carried on upon the rabbit had shown that when platelets are being rapidly produced megalokaryocytes in considerable numbers leave the bone marrow. A majority of these are held up in the lung capillaries where their nuclei form thrombi, while their protoplasm is stripped off and forms the pseudopodial masses and the large forms of platelets found in the rabbit in this condition of rapid platelet production. Other megalokaryocytes slip through the lung and may be found in other organs, particularly in the spleen and in the liver.

[3] J. Morph., 1910, XXI, 2.
[4] J. Exp. Med., 1909, XI, 541.

Through the kindness of Dr. W. H. Welch and of Dr. W. T. Longcope I have been able to examine the lungs of four cases of Hodgkin's disease from the pathological collection of the Johns Hopkins Hospital, and the tissues, including the lungs, from seven autopsy cases from the Pennsylvania Hospital. In none of these eleven lungs, in sections taken from parts uninvolved by the disease, were megalokaryocyte nuclei lacking. In four of the eleven cases they were much more numerous than ever found to be in the human lung in cases of marked leucocytosis, in which their presence to some degree is constant. It is impossible to give exact mathematical values to the numbers in the various lungs because of the varying alveolar expansion in the different specimens. An idea of their frequency may be gained, however, from the statement that in one lung, that of autopsy A-324 (Penn.), no field of moderate magnification (Zeiss: obj., 8; oc., 8) showed absence of megalokaryocytes and the number in such fields varied from three to twelve. Examination of sections of other organs revealed an occasional megalokaryocyte nucleus in the capillaries of liver and spleen—but in no case were they numerous.

That these megalokaryocytes in the lung capillaries come from the bone marrow seems to me certain. There is but one other remote possibility. Examination of a considerable series of gland sections from cases of Hodgkin's disease from a variety of sources, shows that in well advanced cases there is present in the glands, besides the endothelioid giant cells, a type of giant cell indistinguishable from the bone marrow megalokaryocyte. Whether these giant cells are formed *in situ* or are bone marrow giant cells is undetermined. If they should escape into the lymphatics they would also be held up in the lungs. Yet they are so soon enclosed in a fibrous network that their escape in any such numbers as indicated by the lung sections appears improbable. Furthermore a study of bone marrow sections from five of the Pennsylvania series of autopsies seemed to show a definite increase in megalokaryocytes in three. In one was noted an unusual number of small megalokaryocytes, the young forms, showing an activity in this type of tissue in the marrow. All these features with the analogy of the rabbit findings leave, I think, no question as to the origin of the giant cells found in the lungs.

One other bone marrow feature was of interest. In addition to a more extensive pyknosis of giant cell nuclei than is commonly seen, in four of the five marrows was found karyolysis in these cells. This was most marked in a marrow in which there was necrosis of other marrow elements (Penn. Aut. 523), but occurred in the other three marrows where no necrosis of other elements was noted.

In conclusion the findings here presented would seem to indicate that in Hodgkin's disease there is a special activity of the platelet-producing elements resulting in the production of large numbers of platelets and in the emigration of megalokaryocytes in large numbers from the bone marrow. In the lung capillaries these latter are stripped of their protoplasm, which appears in the peripheral blood stream in the form of the masses and pseudopodia described. What part this increased platelet production plays in the disease, I am unable to say. There is in the findings a suggestion that the toxin of the disease acts as sharply upon the megalokaryocytes as upon the lymphoid elements, leading eventually to their necrosis.

These findings are further submitted as additional evidence of the genetic relation between megalokaryocytes and blood platelets.

DESCRIPTION OF FIGURES.

Pseudopodia and megalokaryocytic protoplasm masses from Cases II, IV, V, VII. The figures are camera lucida drawings with the same magnification. The variation in size of the red cells is attributable to variation in the tension under which the smears were spread. In two cases (Figs. 1 and 3) the coverslip method was used in making the smears, in the other two (Figs. 2 and 4) the slide method.

PRIMARY GENERAL PERITONITIS WITH ISOLATION OF THE *BACILLUS LACTIS AEROGENES* IN PURE CULTURE FROM THE PERITONEAL EXUDATE.

By John W. Churchman, M. D.,
Resident Surgeon, The Johns Hopkins Hospital.

Interest in the capsulated group of bacilli (*B. mucosus capsulatus*) has largely centered in the discussion as to the identity of the different members of the group with one another. On this single point a large literature has sprung up, but the question is still to be regarded as only approximately settled. Friedländer's[1] announcement of the discovery of his organism was promptly followed by publications reporting similar, but not identical organisms. These included the rhino-scleroma bacillus (Fisch, Paltauf, and Eiselsberg), the ozaena bacillus (Loewenberg and Abel), the *B. lactis aerogenes* (Escherich) and many others (Fasching, Pfeiffer, von Dungern, etc.). Indeed, Ficke was able to collect from the literature, twenty-two varieties of the organism to which Fraenkel has given the collective name *B. mucosus capsulatus*. There have been many efforts to simplify the matter by showing the identity of some of these forms with one another and redueing them to a few group types. Unfortunately this has not proved an easy matter. Nor has it been possible to simplify the question by applying the serum tests; for all attempts at agglutination have so far failed. (Landsteiner[2]).*

* Von Eiseler and Porges (Centralbl. f. Bakteriol., 1906, XLII, p. 660) claim to have differentiated the ozaena bacillus and rhino-scleroma bacillus from the bacillus of Friedländer by agglutination and precipitation with immune sera.

While there cannot, then, be said to be complete agreement on the subject the conclusions of Wilde represent approximately the majority opinion of bacteriologists; and they have the very great value of standardizing these organisms so that intelligible description of the various forms is possible.

Wilde[3] assembles the numerous varieties of the *B. mucosus capsulatus* under five type groups with the following distinguishing characteristics:

1. Type: *B. lactis innocuus.*

Raised, rounded, porcelain-like colonies on gelatin plates, or colonies like those of *Bact. coli.* No gas formation in glucose agar, alkali formation in milk-sugar bouillon, no coagulation of milk, no indol formation, grey-brownish growth on potato (without formation of gas), very slight pathogenicity for animals.

2. Type: Scleroma bacillus.

Mucoid, raised, colonies on gelatin plates, no gas formation in glucose agar, no (or very slight) acid formation in milk-sugar bouillon, no coagulation of milk, no indol formation, bright grey, translucent growth on potato (occasionally with acid formation), moderate pathogenicity for animals.

3. Type: *B. pneumoniae Friedländer.*

Raised, porcelain-like colonies on gelatin plates, gas formation in glucose agar, acid formation in milk-sugar bouillon, no coagulation of milk, no indol formation, creamy yellowish growth on potato (usually with marked acid formation), moderate or great pathogenicity for animals.

4. Type: *B. aerogenes.*

Raised, or flat, colon-like colonies on gelatin plates, abundant gas formation in glucose agar, acid formation in milk-sugar bouillon, coagulation of milk, no indol formation, abundant growth on potato (with gas formation), marked pathogenicity for animals.

5. Type: *B. coli immobilis.*

Flat, colon-like or raised colonies on gelatin plates, gas formation in glucose agar, acid formation in milk-sugar bouillon, coagulation of milk, formation of indol, gas formation on potato variable, moderate or marked pathogenicity for animals.

From this it will be seen that the bacillus of Friedländer is not regarded as identical with the bacillus of scleroma but is distinguished from it by its ability to form gas in glucose agar; nor with the *B. lactis aerogenes,* which has the power (not possessed by the bacillus of Friedländer) of coagulating milk. Wilde recognizes the existence of intermediate forms; but thinks the attempt to distinguish them as separate species unnecessarily confusing; and suggests these rather sharp distinctions as a useful basis for description. Strong[4] attempts even greater simplification by recognizing only two groups, as follows:

1. Friedländer Group: Easily stained capsules, in tissues and exudates; pseudo-capsules occasionally in artificial media: gas production most abundant on saccharose; slightly less on glucose, little or none on lactose: *no coagulation of milk.*

2. Aerogenes Group: Capsules difficult to stain and inconstant; no pseudo-capsules in artificial media: more abundant and constant gas formation on all three media; *rapid coagulation of milk:* equal amounts of acid on all three sugars.

Grimbert and Legros[5] go even further, claiming that the bacillus of Friedländer and *B. lactis aerogenes* are identical. All forms of both bacilli which they examined coagulated milk in from forty-eight hours to five days; and they cite Denys and Martin[6] as having shown that the bacillus of Friedländer, even if unable to coagulate milk at first, may acquire this characteristic by successive passage through this media.

It will thus be seen that there is justification for regarding the various members of the capsulated group as nearly, if not quite, identical; but that if any distinction is to be made a capsulated bacillus which produces gas in glucose and coagulates milk should be called the *B. lactis aerogenes.** This has been my warrant for the name given to the organism here reported as found at operation in the exudate of a primary peritonitis.

Though the specific nature of the bacillus of Friedländer as the cause of croupous pneumonia could not be established, the pathogenicity of the capsulated group has long been recognized. For laboratory animals it has often been found fatal, though its variable virulence has been again and again emphasized. The discussions as to the distinctions between the various members of the group have rather overshadowed interest in its relation to human disease; but isolated reports of its occurrence in various pathological conditions have continued to appear. In 1895 Étienne,[7] a year later Hébert[8] and two years later Léon[9] collected the literature on this subject. None of these publications are absolutely complete; and several reports of the occurrence of a capsulated bacillus in human disease have since appeared.

The following table contains a complete list of the diseases from which the *B. mucosus capsulatus* has been isolated and thus renders the literature on its pathogenicity readily accessible:

TABLE.

Diseases from which the *B. mucosus capsulatus* has been isolated. The organism has been reported as the bacillus of Friedländer; but also as the rhino-scleroma bacillus, and the *B. lactis acrogenes.*

Aphthous stomatitis	(Cited in review by Étienne[7]).
Purulent rhinitis.	"
Rhino-scleroma.	"
Purulent parotitis.	"
Purulent dacryocystitis.	"
Ulcer of the cornea.	"
Phlegmon of the orbit.	"
Purulent otitis media.	"

* Or, *B. coli immobilis,* according to Wilde; the two are distinguished by the ability of the latter to form indol.

Bronchopneumonia (Cited in review by Étienne[7]).
Empyema (Dieulafoy[43] has reported pyopneumothorax due to gas-producing organisms, without any connection with the lung). "
Serous and purulent pericarditis. "
Simple and purulent meningitis. "
Angiocholitis. "
Pyelonephritis. "
Pyaemia. "
Septicaemia. "
Ulcerative endocarditis. "
Acute lobar pneumonia (Curry[10]).a
Gangrene of the lung (Fortineau[11]).
Membranous bronchitis (Léon[9]).
Osteomyelitis (Schlagenhaufer[12]).b
Abscess of the brain (Sachs[13]).
Pseudo-membranous angina (Hébert[8]).
Salpingitis (Schenk[14]).
Endomyocarditis (Josserand and Bonnet[15]).
Abscess of scrotum (Halban[16]).
Cystitis (Montt-Saavedro[17]).
Purulent conjunctivitis (Kiesentzki[18]).
Empyema of Antrum Highmorii (Howard[19]).
Epidemic exfoliative dermatitis (Russell[20]).c
Hemorrhagic sepsis (Blumer and Laird[21]).d
Hemorrhagic sepsis of new-born (von Dungern[22]).e
Typhus exanthemicus (Hlava[23]).
Cholecystitis (Christian[24]).
Bacteriuria (Wartburg[25]).f
Liver abscess (Ranzi[26]).
Peri-deferential abscess (Macaigne and Vauverts[27]).
Gastro-enteritis (Fricke[28]).g
Tonsillitis (Curry[29]).
General gaseous emphysema with gas cysts of brain (Howard[30]).h
Peritonitis.i

There is then, abundant justification for Hébert's claim that the bacillus of Friedländer must be included in "la catégorie des microbes à tout faire"; and that, along with the staphylococcus, the streptococcus, *B. coli communis,* and *B. pyocyaneus, B. mucosus capsulatus* must be regarded as a saprophyte which becomes an infectious agent when its virulence is increased or the resistance of the host diminished.

It is striking that in the lists, given by Hébert, and by Léon of pathological conditions caused by the capsulated bacillus, no mention is made of peritonitis; and it is certain that a peritonitis of this origin must be both relatively and absolutely, quite rare. The present case is unique in that the *B. lactis aerogenes* was grown from the peritoneal exudate during life in a case of primary peritonitis. The word "primary" is used in the sense of Flexner[31] who suggested this term for that interesting group of cases in which an "inflammation (usually diffuse) of the peritoneal cavity occurs without the mediation of any of its contained organs"; or without any operative or other interference. It may arise independently (spontaneous peritonitis) or may accompany infections in distant parts of the body. Twelve of the one hundred and six cases examined by Flexner at autopsy, were of this variety; and the condition, though a rare one, is well recognized by surgeons.

Onset of illness suddenly two weeks before admission; acute, severe abdominal pains with nausea but no vomiting; then continuous pain, with exacerbations. No jaundice. T. 105.5° F. P. 120. Leucocytes 17,000. Pelvic examination negative. Signs of general peritonitis. Diffuse exudate found in peritoneum at operation. No source found for the infection. Appendectomy, drainage. B. lactis aerogenes in pure culture from the peritoneal exudate. Blood cultures negative. Slow convalescence; pulmonary complication (probably tuberculosis). Recovery.

History.—The patient was an unmarried colored girl, eighteen years old, a nullipara, with normal menstrual, and negative previous history. Two weeks before admission she had been suddenly awakened by severe, knife-like epigastric pain. This soon subsided, but some abdominal pain had been present from the onset to the time of admission to the hospital; and there had been several returns of the acute paroxysms experienced on the first night of the illness. She had also complained of some pain in the left hypochondrium. She had never vomited, but had been slightly nauseated. No jaundice.

On admission, the patient was suffering intensely from abdominal pain. Temperature 105.5° F., pulse 120, leucocytes 17,000. The abdomen was uniformly distended and the respiratory movements greatly restricted throughout. No visible peristalsis. The left lower quadrant was free from tenderness, which was, however, present in the left upper quadrant. Very slight rigidity of the rectus and oblique muscles on the left side. There was definite tenderness throughout the right side—quite marked at MacBurney's point (where there was muscle-spasm), but so exquisite in the right upper quadrant and accompanied by such spasm of the rectus as to make further palpation here impossible. No mass could be felt anywhere. On percussion, dulness was made out in both flanks; the rest of the abdomen was tympanitic. The liver margin was about 1 cm. above the costal margin in the right mammillary line. There was a profuse vaginal discharge (containing Gram negative intra-cellular diplococci) and ulcers on the labia. The vulva was marital but pelvic examination was negative. An exploratory laparotomy was immediately done through a right rectus incision. A considerable quantity of turbid fluid was found free in the peritoneal cavity. The abdominal viscera were uniformly injected, but there was no fibrin present, though the serosa of the intestines was quite red and did not glisten. The appendix and gall-bladder shared in the general inflammation; but were otherwise normal. The Fallopian tubes were quite red, but not distended and no pus could be pressed from their fimbriated extremities. The appendix was removed and two drains placed in the pelvis. Two days after the operation the patient began to cough. Her temperature re-

a The relation of the organism to pneumonia is here discussed.
b Streptococci were also found in the smears from this case; but the bacillus of Friedländer grew out in pure culture.
c The organism found was similar in many, but not in all, respects to the bacillus of Friedländer.
d The cultures were made after death.
e The bacteriological report is very deficient.
f Appeared with fever, chills and headache; symptoms left in three days; bacteriuria finally disappeared under urotropin.
g Organisms found in the stools; presence of B. Friedländer as normal saprophyte in the intestines doubtful; Fricke, Lembke, Germano and others were unable to find it.
h Perkins (J. Exp. M., Jan., 1901) reports a laboratory epizootic among guinea pigs, associated with emphysema of liver, spleen and kidneys, from which the *B. mucosus capsulatus* was isolated.
i These cases receive separate consideration below.

mained elevated, and convalescence proceeded very slowly. The peritoneal symptoms gradually diminished; but signs and symptoms of lung involvement increased.

Blood cultures were done on two occasions, and were negative, as was also the Widal test.

One month after the operation she was transferred to the medical service. Her operative wound was then practically healed, her peritoneal condition negative; but there was a persistent cough with profuse, pale green muco-purulent expectoration. Her leucocytes were 12,600. Her respirations were rapid and shallow, expansion was limited over the left upper front; the percussion note was high pitched in the inter-scapular region, below the angle of the scapula, and in the lower axilla. There was also some impairment over the lower right lobe. The breath sounds were harsh over both fronts, enfeebled over the backs below the spines of the scapulae, but nowhere absent. Expiration was prolonged and numerous fine râles were heard. The patient gave a first degree positive reaction to tuberculin in the left eye. Repeated examinations of the sputum for tubercle

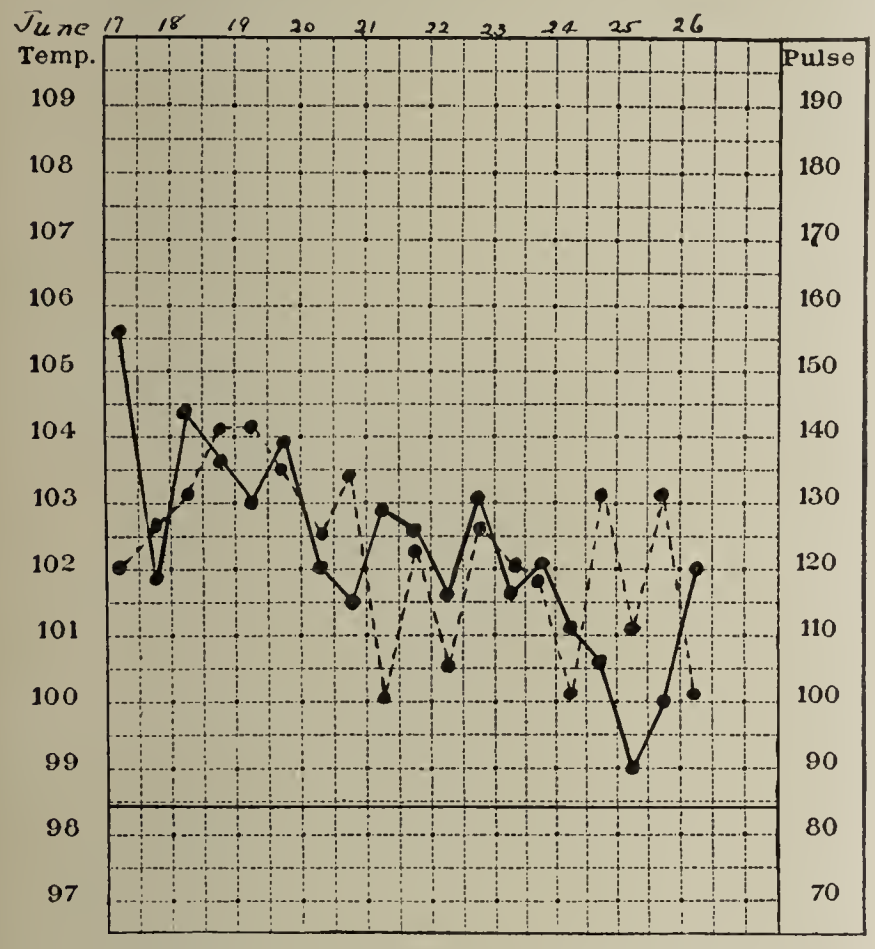

Chart for First Ten Days After Operation.
Solid line = temperature.
Broken line = pulse.

bacilli were negative. The Wassermann test was also negative.

The patient slowly improved and was discharged with a normal temperature, though signs of lung involvement persisted.

The accompanying charts (condensed from the regular temperature and pulse charts of the first and the final days of her illness), indicate the course of the disease.

Cultures made from the peritoneal exudate at operation showed an abundant, dirty whitish growth on agar. The organism was a bacillus of varying size, non-motile and Gram negative. Capsules were readily stained. Gas was formed on potato and in glucose agar. After forty-eight hours, there was acid formation in milk but no coagulation. Slight coagulation occurred in five days; complete coagulation in nineteen days.

This finding, though rare, is not entirely without precedent. No one, however, has reported the organism from a primary peritonitis in cultures made during life.*

The cases of peritonitis, to be found in the literature, in which *B. mucosus capsulatus* was reported as the cause are the following:

1. Breinl [32]: Great hyperplasia of the lymphatics of the small intestine; death from intestinal perforation. In the pus a capsulated bacillus was found which was Gram negative but did not coagulate milk. It was pathogenic for white mice.

2. Fraenkel [33] reports the bacteriological findings (apparently at autopsy) in thirty-one cases.

The following members of the capsulated group were found:

B. lactis aerogenes.

1. Peritonitis from perforation of caecum.
2. Peritonitis with suppurative cholecystitis.

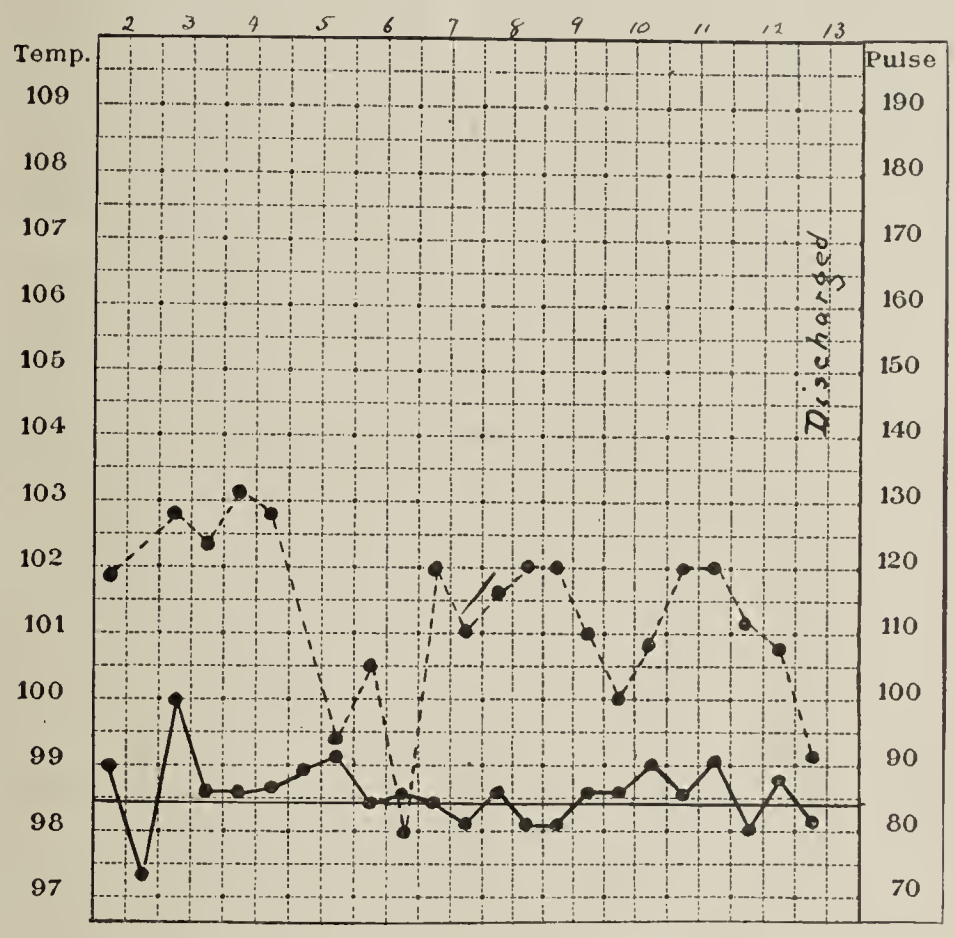

Chart for Last Days of Illness.†
Solid line = temperature.
Broken line = pulse.

B. lactis aerogenes with a *Diplococcus pneumoniae.*

3. Sero-fibrinous peritonitis with nephritis.

Organism resembling *B. lactis aerogenes.*

4. Purulent peritonitis with pyelo- and para-nephritis.

3. Howard [19]: a. Male dead after castration. Multiple abscesses of both kidneys; peri-rectal abscesses opening into cul-de-sac; fibrinous peritonitis. Cultures from peri-rectal abscess, peritoneum, heart's blood, spleen and renal abscesses

* There is good reason for supposing that all the cultures in Howard's cases were taken post mortem, though it is not, I think, definitely so stated.

† The high pulse throughout may have been accounted for by the enlargement of the thyroid which was present. There was also a definite tremor of the hands and a von Graefe's sign.

showed a capsulated bacillus, *which did not decolorize by Gram.* (Decolorization by Gram's method is an essential characteristic of this group of bacilli.)

b. Girl with chronic peritonitis; peritoneal cavity contained large amount thick, creamy pus from which a pure culture of the bacillus of Friedländer was obtained. (It is not stated that this culture was obtained post mortem; nothing said about appendix or tubes, or as to the origin of the infection.)

c. Man, dead of acute croupous pneumonia. Acute general fibrino-purulent peritonitis found. Cultures from pneumonic areas, peritoneum (and elsewhere) showed the bacillus of Friedländer.

d. Ranzi[26]: In the case of liver abscess already referred to (multiple liver abscesses, general peritonitis and endocarditis were found at autopsy), the bacillus of Friedländer was isolated in pure culture from the abscesses, the peritoneal exudate and the cardiac vegetations.

The rarity of this organism in peritoneal infections is illustrated by its absence from the series of one hundred and six post mortem examinations reported by Flexner.[31]

In addition to its other better known pathogenic properties the *B. mucosus capsulatus* is, then, to be thought of in connection with five groups of cases.

1. *Peritonitis.* Cases of Breinl, Fraenkel, Howard, Ranzi [a] and Churchman.[b]

2. *Hemorrhagic Sepsis* (Infectious purpura). Cases of Blumer and Laird, Howard,[34] Neumann,[35] von Dungern [22 c] and Léon.[9]

4. *Liver Infections.* Cases of Ranzi, Canon,[36] [d] Wicklein,[37] [e] Kockel,[38] [f] Wright and Mallory,[39] [g] Clairmont [40 h] and Étienne.[7] [i]

5. Pseudo-membranous angina.[k]

6. Diseases of the Eye.[l]

This patient was treated in the service of Dr. W. S. Halsted, to whose liberality I owe the opportunity of reporting the case. To the kindness of Dr. C. G. Guthrie, I am indebted for the bacteriological examinations made.

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[a] In these four the organism was found post mortem.

[b] Organism found during life.

[c] Bacteriological report deficient.

[d] Septicaemia starting from abscesses of gall-tracts.

[e] Organism reported as bacillus of Pfeiffer.

[f] Multiple infected liver cysts.

[g] Liver abscess following appendicitis and thrombosis of portal vein. Bronchopneumonia.

[h] Peri-cholecystitic abscesses and acute cholangitis.

[i] Mentions unpublished case of Neller (angiocholitis).

[k] Paris Thesis of Hébert [8]

[l] Perles [41] has demonstrated the marked pathogenicity of the bacillus of Friedländer for the eye. Kiesentzki [18] has reported a case of double purulent conjunctivitis in the new-born due to this organism; and Gourfein,[42] in an experimental research on the rôle of Friedländer's bacillus in ophthalmology found the organism in five per cent of four hundred and fifty cases of conjunctivitis, and in ten per cent of forty cases of dacryocystitis.

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THE SUBMUCOUS RESECTION OF THE NASAL SEPTUM, TECHNIQUE AND RESULTS IN THE WRITER'S PRACTICE.*

By Sylvan Rosenheim, M. D., Baltimore.

The development of this operation rests on principles practiced long before the operation attained any great vogue. Various orthopedic methods had been used to correct these nasal deformities. Many surgeons, among them Trendelenburg, Roux, Juracz and others attempted corrections, using the submucous method. For instance, Trendelenburg separated the movable septum from the upper lip, dissected up the mucosa, and then resected a small piece of cartilage. Among rhinologists Hartman submucously removed in the early days a small piece of cartilage. Peterson did the same making a flap with the base upwards.

To Krieg, however, belongs the credit of putting the operation on a sound basis. His first publication appeared in 1886. His second report in 1889 records 14 cases and improvements in technique. In his third report in 1900 he gives the results of 130 operations and refers to the non-recognition of his work. Krieg's operation consisted in a removal of the deflected cartilage and bone with the sacrifice of the muco-perichondrium and periosteum of one side. He considered the operation at all times very difficult, at times a veritable "Kunststück." The after treatment took a number of weeks; but the results were excellent and in 50 per cent of the cases, external deformities were corrected. There were perforations of the septum in 12 per cent of his cases. In 30 per cent of the cases a preliminary treatment, usually cauterization of the inferior turbinate, rarely resection, was necessary.

Until 1899 the method had not been extensively used as is evidenced by Victor Lange's statement in Heymann's Handbuch that there was no good operative method for the correction of septal deformities. In this year Bönninghaus reported 19 cases and stated that he had been using this method for the last four years. He lays emphasis on the importance and necessity of also removing the bony parts of the deviation. The discovery of the properties of an aqueous extract of the suprarenal capsule on the vascular system by Schaefer and Oliver and others and further work along this line by Abel was quickly followed by the clinical use of this substance. This discovery materially aided the development of this operation as it did of all other operative nasal work.

In America, Otto T. Freer developed this operation along original lines. His first publication in the Journal of the American Medical Association gives E. F. Ingals (1882) credit for originating the type of operation designated by Krieg as the window resection. Freer's work was started in 1901 and he was ignorant of the previous work of Krieg and Bönninghaus. Freer's original method consisted in the making of flaps, the anterior one being held forward so as to thoroughly expose the deviation, and after dissection of the mucosa, in removing the cartilage. He then fractured the cartilage and placed it in a straightened position. In his later publications he states that he has given up the practice of fracturing the bony septum, and instead cuts it away with Grünwald's forceps. For this work he has devised 12 knives which are found to be most useful and necessary. In speaking of making the flaps he speaks of dissecting the mucosa but he probably includes the perichondrium and periosteum in this flap. Comparing this operation with the Asch method, he says "the latter will always be resorted to by the general surgeon who enters special fields without special skill, for the surgeon sins against us far more than the cautious general practitioner anxious for his patient's welfare."

Killian in 1904 published his most exhaustive paper giving the whole detail of the operation in his hands and the results of his cases. His paper marks an important milestone in the development of the operation, inasmuch as most operators at the present time use essentially his method. In a previous paper (1899) he had pointed out that the making of a flap and the use of his long speculum for "rhinoscopia media" materially helped in the operation and lessened the after treatment. He lays great stress in a strict aseptic technique and draws attention to the various contra-indications to the operation. Killian makes a vertical incision about one-half a centimeter behind the movable septum. This incision goes to the cartilage. He next elevates, laying stress on the importance of including the perichondrium in the part elevated. He next perforates the cartilage, using a finger in the other side of the nose to prevent going all the way through to the other side. After elevating the muco-perichondrium of the other side he removes the cartilage with his own cartilage knife or with Hartman's biting forceps. A picture of his cartilage knife readily demonstrates that Ballenger's swivel knife is practically the same with the exception that the knife revolves. Posteriorly the bone is removed with Hartman's biting forceps, anteriorly with Killian's chisel. If necessary the flap is sutured.

About the same time Hajek, Menzel and others published the results of their work and their methods, but they added nothing to that of Killian, in fact they hardly seemed to realize the beauty and the superiority of his work.

From this time on these methods of operating on deformed nasal septa increased in popularity. They were rather late in getting to England notwithstanding its proximity to the country where it originated and was rather extensively used. For instance, in 1901 Mayo Collier remarked that he had seldom or never attempted to straighten the septum; the results were most unsatisfactory, and he preferred to remove a piece with knife, chisel or saw. In 1904, St. Clair Thomson described his results in a number of cases.

There have been various improvements in technique in the

* Paper read before The Southern Section of the American Laryngological, Rhinological and Otological Society, Jan. 21, 1911.

last few years. Ballenger's swivel knife, a modification of Killian's cartilage knife, has simplified the removal of the cartilaginous septum. Hurd, Beck, Carter, Bruning and others have devised various instruments that assist in the operation. To prevent perforations, Gulliver transplants a piece of muco-perichondrium from the redundant side in the perforated spot and holds it there with packs. Ballenger describes another method of avoiding a permanent perforation, which he says he learned from Dr. Goldsmith of Toronto. After resecting the cartilage it is placed in normal salt solution and if there is a perforation produced during the operation, a piece of this cartilage is placed and held there by packs. Yankauer's suggestion to extend the vertical incision across the base of the nose, aids considerably in enlarging the field of operation.

Writer's Method of Submucous Resection of the Deviated Nasal Septum.

The patient enters the hospital on the morning of the operation, undergoing a thorough physical examination. The urine is examined for albumin and sugar. One-half hour before the operation there is administered a hypodermic of one-quarter grain of morphia.

Instruments.—The following instruments are used: Beckman's nasal speculum, probe, applicators, Freer's right and left angular and straight knives, Freer's sharp and dull elevator, Jansen's dull elevator, the writer's specula, Ballenger's swivel knife, Grünwald's and Jansen's biting forceps, Killian's chisel and hammer, dressing forceps, and Worthington's membrane holder.

Technique.—Two nurses are used, and the instruments are sterilized by boiling, the head mirror by the use of formalin vapor. [Photographs show the arrangement of the room and table.] The patient's face is washed with soap and water, alcohol, and bichloride solution. A sterile towel is placed around the head and a sterile sheet covers the body.

Operation.—The septum is cocainized with swabs placed first in adrenalin chloride solution 1-1000, wrung dry and then dipped in powdered cocaine. This is rubbed on both sides and also on the turbinates if these are to be removed at the same time, and in the antral, ethmoid and sphenoid regions, if a sinus operation is also to be performed. Cocainization is very rapid and the writer has not seen a single case of cocaine intoxication by this method in over five years' use of cocaine, whereas such was not infrequent by the pledget method of using cocaine. Also the anesthesia is much more profound especially where sinus work has also to be done. Rarely general anesthesia is necessary, ether being used. After cocainization, long pledgets soaked in a 1-1000 solution of adrenalin and wrung out almost dry, are packed against the septum of both sides and allowed to remain there from five to ten minutes.

The initial incision of Killian is made just in front of the deflected portion and continued outwards across the floor of the nose as suggested by Yankauer. This incision goes down to the cartilage and the muco-perichondrium and muco-periosteum of the convex side is then elevated with the various elevators described. The cartilage is next incised to the perichondrium of the opposite concave side. One soon learns to recognize when the perichondrium is reached and no special instrument or technique is necessary to prevent perforation at this point. If it occurs the method described by Ballenger of inserting a portion of the resected cartilage here can be used, although the author has had no occasion to try this procedure. Next the muco-perichondrium and muco-periosteum of the concave side are elevated. This is often much accelerated and rendered easier by the employment of the author's speculum which is next inserted, one blade on each side of the cartilage, and then opened up as far as possible. By the use of his speculum the field of the following steps is made most plain and visible and any injury of the membrane of either side is prevented (see cuts). The cartilage and bony deflected parts are then removed with Ballenger's swivel knife, Grünwald's and Jansen's biting forceps. The maxillary crest is removed with Killian's chisel. Where the deflection is very acute this method is slightly modified in that the cartilage up to the point of the deflection is first removed, and then the remaining part can be manipulated into a better position for continuing the dissection of the membranes. After all the deflected parts of cartilage and bone are removed the wound is thoroughly cleaned of debris with cotton sponges soaked in normal salt solution. The membranes are then smoothed down after removal of the speculum and the septum examined to find if straight or not. If it is not straight, it is due to insufficient removal of cartilage, bone or bony crest of the superior maxilla, which is removed until the septum assumes a vertical position. The membranes are held in position by Worthington's holder and a pack placed in each nostril, when the membrane holder is withdrawn. These packs are made of strips of iodoform gauze, surrounded with gutta percha protective and are greased with vaseline before insertion into the nose. A number of various degrees of thickness are made for each case and one that fits into the nares snugly is used on each side. They make most excellent packs, are withdrawn without any pain to the patient and without that bleeding which is so annoying after withdrawal of the ordinary gauze dressing. In case sinus work has been done, the protective covering of the pack is perforated in a number of places. If the ethmoid cells have been opened also, a small perforated pack is placed in this region superimposed on the other pack.

After his return to bed, the patient is given a glass of water, containing thirty grains of urotropin to the quart, every hour. He is put on full diet. If there is any headache he is given either migraine tablets, or a powder of acetanilid five grains, codeia sulphate half a grain, and one grain of caffeine citrate. If these are not efficient he is given a hypodermic of one-quarter grain of morphia. The next morning he is given a bottle of citrate of magnesia. The pack on the side opposite the incision is removed at the expiration of 24 hours, and on the side of the operation at the expiration of 48 hours. He is discharged from the hospital on the second day and after the packs are withdrawn is given a spray of Dobell's solution with

enough adrenalin chloride to make a 1-10,000 or 1-15,000 solution for home use. Usually but little after treatment is required in the simple cases. Where an inferior turbinectomy or a sinus operation is performed at the same time, it is necessary to irrigate the nose for some time afterwards.

Writer's Results.

The object of this paper is to give the results up to date in a series of cases in which he has performed this operation. His conclusions are based on his records of over fifty cases. Some earlier cases were dispensary cases of which he has no histories. Some of this small series were also dispensary cases but inasmuch as these received the same attention as the private cases, they are of equal value as statistics. Letters

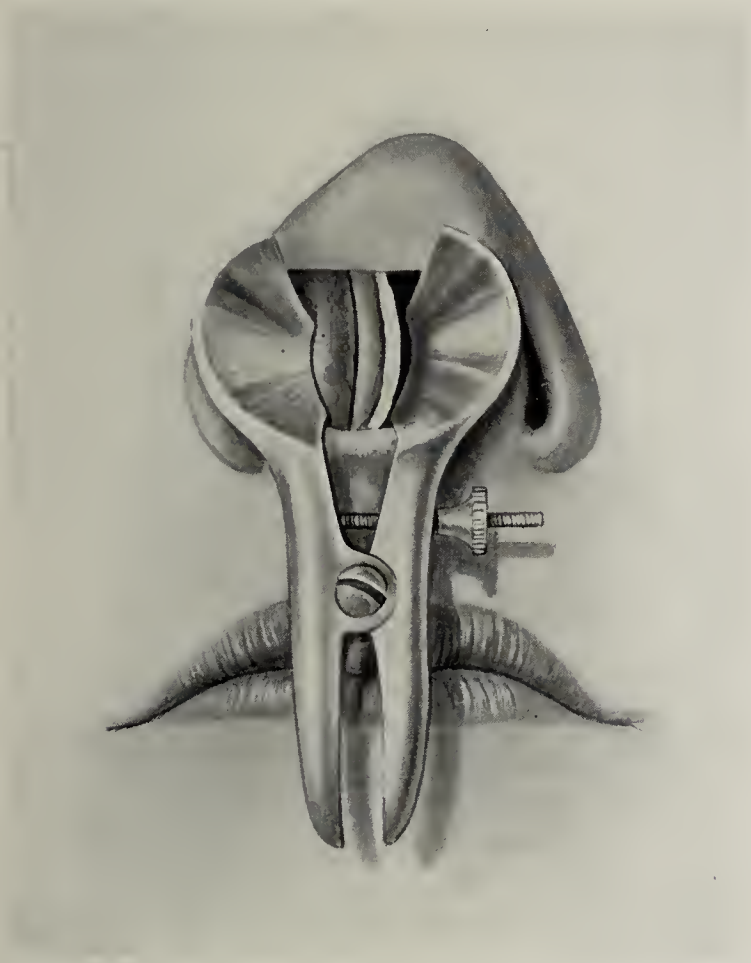

Fig. 1.—Speculum in place, before removal of cartilage and bone.

were written to all of the patients to return for examination to determine whether there had been any difference in the result as considered for a short time after the operation. Unfortunately only a small percentage have seen fit to appear (twenty-three). Letters have been received from seven which are of some value.

I shall first enumerate the results in these cases at the time of their discharge and then give the further observations based on those patients who have returned for examination or who have written.

Regarding the ages of these patients, all but four of the early cases are over fifteen years of age. One patient was ten, another twelve, and two were thirteen years old. Owing to the fact that we do not know what effect this operation will have on the development of the nose, I have thought wisest not to operate on young children unless the breathing is absolutely cut off. In such cases it might be well to endeavor to improve the septal position by widening the palatal arch as suggested by Black, Brown, and others. So far I have seen but one of these young patients after the lapse of any time. This patient was a boy aged 13 years, on whom a submucous resection of the septum and later a double inferior turbinectomy was performed. Now, over three years later, the good result obtained at the time of the operation still continues; the breathing space is good, and the nose, he thinks, has rather improved in shape.

In about half of my cases a simple submucous resection was performed and in nearly all the rest either the inferior turbinate of one or both sides was removed in part. In one case, the anterior ends of the middle turbinates were resected. In three cases extensive sinus work was performed at the same

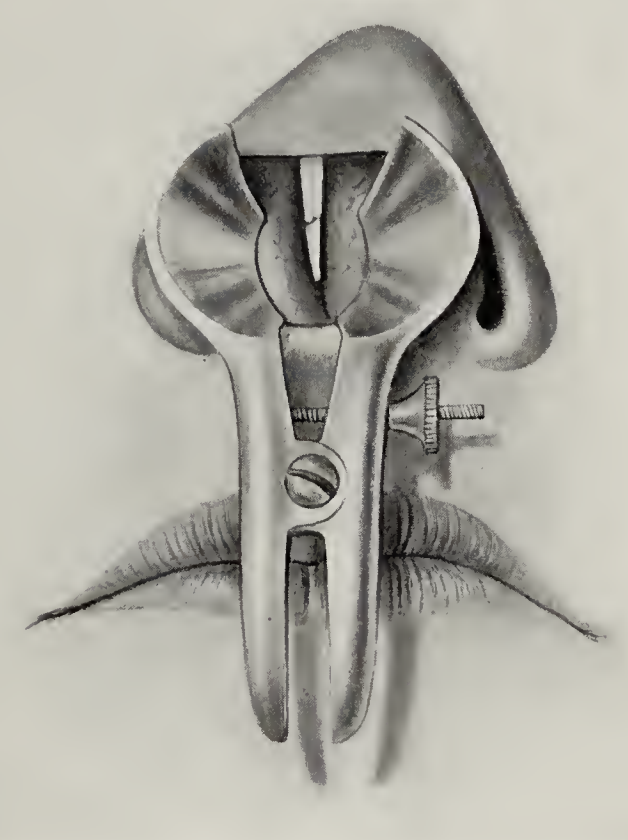

Fig. 2.—Deflected bone and cartilage removed. Posterior part of vomer and perpendicular plate of ethmoid visible.

time. In one case a hump on the dorsum of the nose was also removed by an external incision.

Reaction Following Operation. Infection.—I had always considered the submucous resection of the septum, an operation with no risk of mortality until I received a report from H. Hays, in which he described two cases of infection, resulting in one case in meningitis and death. Purcell also mentions one death following infection. As practically all these cases were done in the hospital the temperature charts have been at my disposal for accurate observation; also I have seen all of the cases for long enough times after the operation to make my following remarks absolutely accurate.

The temperature charts of my cases, to all but a few of which I have had access, show in most either a normal temperature or a rise of about one degree on the following day which quickly subsides after removal of the packs and clearing of the bowels. In one case the rectal temperature rose

to 102.5° F. and in another 103.4° F. but in these cases the temperature subsided in about 24 hours to normal after removal of the packs and calomel purgation. I have two cases of slight infection to report. In one case, an incomplete submucous resection was done by one of the house surgeons—his first case. Four days later the patient was readmitted to the hospital with a red swelling on the side of the nose which proved to be erysipelas, a mild attack, which quickly subsided. Examination of the nose revealed an incomplete removal of the cartilage and a small perforation of the septum and the septum somewhat swollen. One month later a more complete submucous resection was performed with excellent result. The day following the operation, the temperature went up to 102.6° F. (rectal) but fell to normal in 24 hours. In another case there was a slight infection between the membranes with slight swelling and slight elevation of temperature. A small amount of grumous material was scraped out through the original incision and a counter incision made in

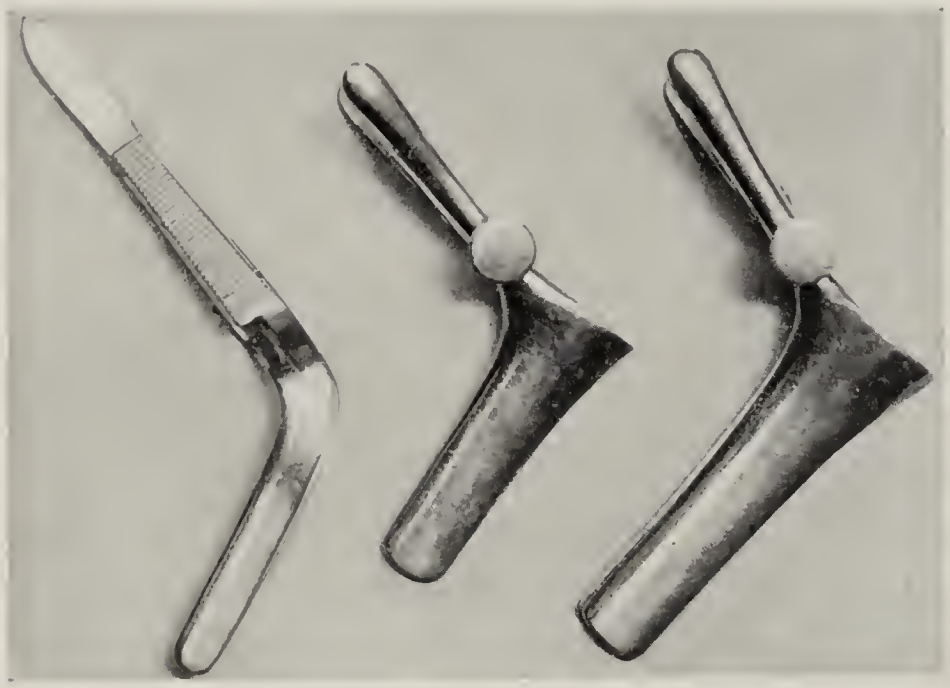

Fig. 3.—Worthington's flap holder, and author's speculum (two sizes).

the septum, a little posteriorly. This discharged pus for about a week and then closed, leaving a clean septum, with no perforation. This case has been attended by no other bad result—such as sinking of the bridge of the nose.

Results in General.—In general, the results may be termed excellent. The main cause for this operation, difficulty in breathing through the nose, has been relieved in all cases but one, and in that case failure was due to a projection of the end of the quadrangular cartilage outside the nose on the side opposite the side of the deflection. This was not removed at the operation and on removal of the packs the cartilage reassumed a deflected position. Unfortunately this was an out of town patient and I have had no further opportunity to correct the work. The lesson from such a case is to operate from both sides, dissecting out the anteriorly placed deflection through an incision made in the cutaneous septum. Although no particular attempt was made in any of the cases to remedy external deformities, these were in many cases much improved as is shown by the rough casts of one case. These plaster casts are not difficult to make and once made, constitute an excellent method of ganging the result in this particular. In one case headaches were entirely relieved. A severe neuralgia of the side of the face to which the septum was deviated, has been entirely relieved for three and a half years following the operation in another case. A general improvement in health was noted by many.

Perforation of the Septum.—I have notes of perforations in four cases; three of which were very small and one being fairly large. In the last case, done some years ago, the deviation, as shown by the plaster cast, was very extreme, forcing outward the nasal bone of that side. I take it, however, that a perforation in this case could either have been avoided or would have been much smaller by using the method described earlier, namely, first removing the cartilage up to the point of deflection before attempting to dissect the membranes beyond this point. As has been the experience of others, I have observed no scabbing about these perforations nor have they given a patient, who is unaware of them, any discomfort.

Special Results.—One of the objects in reviewing these cases was to determine whether there occurred after the lapse of some time any bad after effects, such as sinking of the bridge of the nose. I also wished to get some evidence regarding the reformation of the cartilage and bone removed.

Depression of the Bridge of the Nose.—An early report by Sheedy of a number of cases of a sinking in of the nose following this operation made me particularly apprehensive in this regard. A later report by him is to the effect that now he seldom sees this deformity and thinks the former bad results were due to too extensive removal of cartilage. As the immediate result of the operation, I have not seen such a result. I have seen or heard from twenty-nine patients on whom I have operated from over four years ago to the present time. In not a single case was there a trace of any secondary sinking of the bridge of the nose. Several of these patients had syphilis which had been thoroughly treated and these did as well as any of the cases.

Reformation of the Septal Cartilage and Bone.—At the present time I can report on but eighteen cases in regard to this point. In all, the septum had regained firmness but in none could one say that there was complete reformation of the cartilage and bone. In some there was a large area, quite soft and movable to the probe; in others this area corresponded only to the center of the place from which the cartilage had been removed. Some of the more recent cases were firmer than the earlier cases. It is possible that this is due to not having included all of the perichondrium and periosteum in the early cases.

Conclusions.

1. The submucous resection of the nasal septum is a method by which all varieties of deflections of the septum can be corrected.

2. It is probably better for us to be cautious in the case of young children and do the operation only when it is urgently demanded.

3. Chronic sinus infections are not a contra-indication; in fact this operation is often a necessary accompaniment in order to complete the sinus work and obtain free drainage. Such operations as well as inferior or middle turbinectomies are best done at the same time.

4. Luetic individuals who have been well treated and show no signs of the disease, yield as satisfactory results as others.

5. It is absolutely essential to have strict asepsis in all the details of the work.

6. Infections following this proeedure should be as infrequent as in any other operation carried out with aseptic technique, and the operation considered both safe and satisfactory.

7. Perforations of the septum may be caused infrequently but they are of no consequence and cause the patient no discomfort.

8. There is no reason to fear sinking of the bridge of the nose, following at any time after the operation. On the other hand, external deformities which may be present are frequently relieved.

9. While it is possible that there may be, to a slight extent, new cartilage or bone formed after the operation, this is never complete.

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THE GROWTH OF EMBRYONIC CHICK TISSUES IN ARTIFICIAL MEDIA, AGAR AND BOUILLON.

By Margaret Reed Lewis

and

Warren H. Lewis, M. D.

(*From the Anatomical Laboratory, The Johns Hopkins University.*)

In 1908, working under Dr. Max Hartman at the Kgl. Institut für Infectionskrankheiten in Berlin, one of us found that bone-marrow from the guinea-pig formed a membrane-like growth with mitotic figures on the surface of nutrient agar. This agar was a modification of one used at the Institute for the cultivation of amœba. In the place of distilled water a modification of Locke's modification of Ringer's solution was substituted.

Last fall we began the cultivation of embryonic pig bone-marrow in the blood plasma of older pig embryos. We utilized very much the same methods as were described by Burrows and Carrel, but without very conclusive results. We attempted to start our cultures from a very few cells instead of small pieces of tissue.

With the appearance of the important publications by Burrows and Carrel on the cultivation of the tissues of warm-blooded animals in clotted plasma adopted by Burrows from Harrison's brilliant discoveries on the growth of amphibian tissues, especially nerve axons in clotted lymph, we began similar studies on embryo chicks of various ages and were able to obtain by the method of Burrows and Carrel very wonderful growths from the various organs of the embryo.

The blood of adult chickens was used. It was taken from the external jugular vein, which lies just beneath the skin of the neck by means of a glass canula coated with paraffin, instead of oil, and was allowed to flow into paraffin-lined tubes, cooled in a freezing mixture, centrifugalized, the plasma drawn off and kept in paraffin-lined tubes in the ice box. We have obtained excellent growths with plasma two weeks old. Instead of sealing the hanging drops with paraffin, we find vaseline, which has been in the autoclave more satisfactory.

Not only were growths obtained in hanging drops, but much more extensive ones were obtained in Petri dishes, the diameter of these growths sometimes exceeding 1 centimeter. The Petri dishes must be kept in a moist chamber to prevent drying. The Petri dish method affords certain advantages for experimentation on the growth, which can be subjected to the influence of various fluids for varying lengths of time. We have obtained beautiful results with some of the vital stains, especially neutral red.

We have not found it necessary to dissect the chicks in a warm chamber, provided one works with sufficient rapidity in transplanting. Our observations have been made with the use of the warm stage, which seems quite satisfactory. Good growth takes place at temperatures varying from 34°–42° C.

There is great similarity in the growths from pieces of liver, intestine, heart, brain, kidney, adrenal, muscle, stomach, thyroid, retina, cornea, etc., of chick embryos from 10 to 21 days old. Radiating strands, migrating cells, membrane formations and vesicles or loop-like places seem to be common to all. The spleen, however, usually sends off migrating cells alone for some time after the culture is made, and only later do the radiating cells appear, if they appear at all.

The general similarity in the growths from the various organs seems to lead to the conclusion that the growing tissues are only such as are common to the various organs, namely, connective tissues of various kinds and endothelium of the blood vessels. We have been able to trace, in some fixed and stained specimens, the endothelium from the blood-vessels of the original piece out into the new growth where the cells of the endothelial radiations closely resemble the cells of the other radiations found there.

Recently we have succeeded in cultivating small pieces of embryonic chicks in a nutrient agar both in hanging drops and Petri dishes. The growths have, as a rule, not been so extensive as those in the plasma, but otherwise resemble them. Some specimens show radiations, others membranes and reticular formations with migration of cells. Mitotic figures are found in the stained preparations. The cells often show long irregular processes and move outward from the old piece. The following medium has so far given the best result with chick tissue:

Ringer		10 cc.
NaCl	.9 gm.	
KCl	.042 "	
$CaCl_2$	.025 "	
$NaHCO_3$	.02 "	
H_2O	100 cc.	
Agar	.25 gm.	
Bouillon		2 cc.
NaCl		.0675 gm.

Into a hanging drop of this medium we transplanted two small pieces from the liver of a nine-day chick embryo. Within 24 hours cells began to radiate and migrate from the smaller piece into the surrounding medium. In 48 hours the growth had exceeded that of the control in plasma and was as extensive as any growth observed in plasma from such a small piece, less than $\frac{1}{2}$ mm. in diameter. The entire growth at the end of 48 hours was four times the diameter of the original piece and could readily be seen with the unaided eye.

The specimen was fixed when 48 hours old in osmic acid vapor and stained with Ehrlich's hematoxylin and eosin. All stages of mitosis are present in the new growth; as many as 10 mitotic figures were counted in one field under the high power.

Small pieces of transplanted intestine, about 1 mm. long, from a 20-day chick embryo, continued in regular peristalsis for over 48 hours in the nutrient agar.

We have obtained growth in the nutrient agar containing from .9% to 1.58% of NaCl, 10% and 20% bouillon with .25% and .5% agar.

More recently still we have obtained active growth and migration of cells in a fluid medium as follows:

Ringer			
NaCl	.9	gm.	
KCl	.042	"	
$CaCl_2$	.025	"	5 cc.
$NaHCO_3$	.02	"	
H_2O	100	cc.	
Bouillon			5 cc.
NaCl			.045 gm.

The migrating cells in this fluid medium are often irregular with long slender processes almost exactly like those we have seen in plasma media. The cells are active, sending out and retracting their pseudopodia, and sometimes moving slowly apparently on the under side of the coverslip. Some of the transplanted pieces also show radiations.

Shorey reports the growth of nerve fibers of Necturus in a nutrient gelatin, but no notice of an active proliferation or migration of cells was contained in her description.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

Meeting of October 17, 1910.

Dr. Louis Hamman presiding.

Employment of Radium as an Aid to Surgery in the Treatment of Cancer, Angioma and Keloid.* Dr. Louis Wickham, Paris, France.

The destruction by burning, which is chiefly sought for by many radium-therapeutists, is not of great interest, since similar results can be obtained by many other agents.

The most interesting and important aspect of radium as a therapeutic agent is the selective action of the rays. Here radium plays the rôle of a subtle modifying agent, which goes to seek out those elements which are the most sentitive to its action. All morbid conditions are not suitable ground for this selective power; the most favorable are cancer, angioma, keloids, eczema, and other diseases.

The exact meaning of "selective action" is that a certain quantity of measured radio-activity can modify the cancerous cells and arrest their malignant evolution, without producing any modifying action on the normal cells surrounding the cancer, thus enabling a cancer to regress and disappear without producing on the surface any signs of irritation or inflammation.

This selective action can work either on the superficial or the deep seated pathological tissues, the rays possessing the power of traversing them. The determining cause between the caustic action which burns, destroys, and the selective action is the *quantity* of rays absorbed in a given time by the tissue. If large quantities of slightly penetrative rays be employed, the result is a superficial necrotic action; but if the quantity be measured, a selective action without any irritation can be secured.

If a large quantity of superpenetrative rays be used a deeper necrotic action follows, but let the quantity be measured, a selective action in the deep seated tissues without any irritation is the result.

Dr. Wickham here showed a series of lantern slides representing histological sections of fragments taken from a voluminous cancer of the breast (lobulated epithelioma) where the selective action of the rays was demonstrated. In this case this selective action was visible on fragments taken even from a depth of nine centimeters, a depth which, up to now, had not been deemed affectable by the radium rays.

The depth at which radium works depends on the quantity of radioactivity employed which in this case was 19 cgr. of pure radium applied for 48 hours at one point.

Dr. Wickham laid stress on the importance of acting simultaneously on, or in, several points of the tumor by his "cross-fire" method in order to concentrate the greatest possible quantity of rays on the points in the deep-seated tissues so that the rays may act with greater homogeneity.

He showed, by means of lantern slides, cases, treated in collaboration with Dr. Degrais, of grave cancer, angioma, and keloids, in which the regressions were very remarkable.

The methods for the treatment of cancer by radium, that he has established with Dr. Degrais, joined to other methods of using radium as a therapeutic agent have led Dr. Wickham to the following conclusions:

* Abstract of a paper read before the Johns Hopkins Hospital Medical Society, October 17, 1910.

1st. The excellence of the results cannot exist without long experience and a profound knowledge of the methods to be used, and principally without a large quantity of radium.

2d. In the majority of cases surgery should be associated with the use of radium.

The radium-therapeutist, in the presence of a case of grave cancer, must first consult a surgeon in order that the patient may not be deprived of the prompt help of surgery.

If surgery is confronted with a case difficult or impossible to operate upon, radium can be applied *before hand,* in order to prepare the ground, or *afterwards* in combination with operative measures. Surgery ought to be utilized for making the perforations, incisions or partial extirpations which diminish the thickness of the tissues and render more effective the action of the radium introduced into the wounds.

Surgery should be also employed for opening a way for radium through artificial orifices or for conducting the tubes of radium to the tumors through the natural orifices. It is under such conditions that Dr. Wickham has treated cancers of the œsophagus, of the neck, of the bladder, of the intestines, of the rectum, of the larynx, of the uterus, subcutaneous and deep-seated cancers, cancers of the breast, etc. Dr. Wickham related the history of several cases of cancer which, normally would have succumbed in 2 or 3 months, but which are still, after one year, having their condition ameliorated. Surgery should develop its ingenuity for finding operative means of helping to apply the radium so that it will penetrate to the seat of the tumors, above all when these are of difficult access.

3d. The tumors should be inundated by the rays, and to this end the apparatus chosen should be the most powerful possible, and so numerous that the different radium containers may be employed in opposition, either on the exterior of the tumor, or in the interior after perforation. If there is any skin, mucous membrane, blood vessel, or nerve to protect, there must be placed between the apparatus and the tissues, metallic screens (aluminum, lead) whose thickness varies in proportion to the amount of radioactivity needed, and the duration of the application. This is the method of filtration that Dr. Wickham inaugurated in 1905, which is very useful when strong action in the depth of the tumor is needed, to prevent injuring the surface. The apparatus can be employed with very thin filters when it is important to utilize the maximum quantity of rays.

4th. Like surgery, radium has neither an action on the general physical condition, nor can it prevent recurrences and metastases. This should be insisted upon in order that the term cure, which on principle should be avoided, may be attributed only to the regression of the tumor itself, and so that there may be no risk of deceiving either the patient or the family physician.

5th. Even thus limited radium is a valuable weapon. In our struggle against cancer we are so badly armed that any new therapeutic agent if it be in some way really effective, as it is in this case, should be taken into serious consideration. By the help that radium brings to those suffering from cancer, it occupies a high place in our esteem and is the principal reason of the gratitude we owe to the discovery and scientific works of savants like Curie, Ramsay and Rutherford.

NOTES ON NEW BOOKS.

Practical Bacteriology. Blood Work and Medical Parasitology, Including Bacteriological Keys, Zoological Tables, and Explanatory Clinical Notes. By E. R. Stitt, M. D., Surgeon U. S. Navy, etc. Second edition. Revised and enlarged. Illustrated. Price $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1909.*)

To the first edition, reviewed in the Bulletin, December, 1909, the author has added a chapter on Poisonous Snakes, and here and throughout the volume has incorporated new material, so that his work is as much "up to date" as possible. Dr. Stitt has crowded too much into this book—and this is its drawback—but it has merits which make it a useful aid to the student, who is willing to use it as a guide only, along with other standard textbooks.

The Harvey Lectures. Delivered under the Auspices of The Harvey Society of New York, 1909-10. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

The lectures by Prof. Richard M. Pearce on "The Problems of Experimental Nephritis," and by Prof. Eugene L. Opie on "Inflammation" have already appeared in the Archives of Internal Medicine, and that by Prof. Magnus-Levy on "Uric Acid in Gout," in the American Journal of the Medical Sciences. The other papers by Professors Huber, Cohnheim, Brodie, Hektoen and Meyer are here published for the first time. Three of these lectures, those by Pearce, Brodie and Huber, deal with problems relating to the kidney; in last year's series there were four on metabolism in connection with which Magnus-Levy's paper should be read. He and Prof. Cohnheim, who discussed "The Influence of Sensory Impressions on Scientific Deductions" were the two notable foreigners who appeared before the society. Dr. Meyer dealt with the much involved problem of "The Present Status of Aphasia and Apraxia," and Dr. Hektoen also treated a very complex subject in his lecture entitled, "On the Formation and Fate of Antibodies.

The Harvey lecturers contribute annually much that is of permanent value to medical science, and the addresses of the past year emphasize the importance of this society.

Treatise on Diseases of the Skin. For the Use of Advanced Students and Practitioners. By Henry W. Stelwagon, M. D., etc. Sixth edition. Thoroughly revised. Illustrated price, $6.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

Between June, 1902, and the present time this work has been reprinted ten times and revised six, which shows the exceptional, but well deserved, success it has had. The last edition is more abundantly and still better illustrated than its predecessors, and the author has added much new text on pellagra, sporotrichosis, oriental sore, gangosa, granuloma annulare and other rare affections, thus keeping his book well up with the latest developments in knowledge and treatment of these diseases. The third edition was reviewed in the Bulletin in August, 1904. What most prac-

titioners desire is a good practical book on skin affections, and in Stelwagon's they will find all the help that can be given them, for there are no diseases more trying than these to both doctor and patient, and none in which no help seems to be forthcoming at times, but with the author's guidance doctors can at least feel certain they are doing no harm, and as much good as anyone, if they make the right diagnosis. That is the difficulty in these diseases, but here also the author is clear in his descriptions, and the simpler affections should be easily recognized after studying his descriptions of them. The rarer ones, when met with, should be referred to a specialist. The book is in every respect thoroughly reliable.

American Edition of Nothnagel's Practice. Diseases of the Intestines and Peritoneum. By Dr. Hermann Nothnagel, of Vienna. Edited with additions by H. D. Rolleston, M. A., M. D., F. R. C. P., etc. Second edition. Thoroughly revised. Price, $5.00. (*Philadelphia and London: W. B. Saunders Company, 1907.*)

The excellencies of this work were noted in the Bulletin at the time of its first appearance (July-August, 1904), and this edition is an improvement on the first. It has been "thoroughly revised" and those already acquainted with Dr. Rolleston's work will be glad to have a chance to see how his views on many points, still awaiting solution, have been modified, and note the changes he has found it necessary to make. Students should be familiar with Nothnagel's Practice, which is a standard work.

Diagnosis and Treatment of Women. By Harry Sturgeon Crossen, M. D., Professor of Clinical Gynecology, Washington University, St. Louis, etc. Second edition. Revised and enlarged. Illustrated. (*St. Louis: C. V. Mosby Company, 1910.*)

The first edition of this work was reviewed in the Bulletin for April, 1908. Since then the author has enlarged his book, and improved his index, and now more than ever the general practitioner will find the volume a most useful one.

Scientific Memoirs. By Officers of the Medical and Sanitary Departments of the Government of India. (New Series) No. 38. *Preliminary Report on the Killing of Rats and Rat Fleas by Hydrocyanic Acid Gas.* By Captain W. D. H. Stevenson, M. B., I. M. S. (Bombay Bacteriological Laboratory.) Price 9d. (*Calcutta: Superintendent Government Printing, India, 1910.*)

The nature of this report is of such a special character that it will not appeal to many readers, but our health officers and others should read it, as all carefully studied means for exterminating the cause of plague should receive serious attention by them.

The Annual Report from the Chemical Works of E. Merck of Darmstadt (Ger.), which has just appeared, contains much interesting information "of recent advances in pharmaceutical chemistry and therapeutics." Eighty-five pages are devoted to "Serum Therapy and Bacteriotherapeutic Preparations," and about 250 to new preparations and drugs. The therapeutist and pharmaceutist, when desirous of information about the newest chemical preparations, will find this report a useful and reliable one.

The Modern Treatment of Alcoholism and Drug Narcotism. By C. A. McBride, M. D., L. R. C. P. & S. (Edin). Price $2. (*New York: Rebman Company, 1910.*)

Physicians in charge of sanatoria for the care and cure of inebriates, and others addicted to various drugs, will be glad to have this volume on their shelves. The author has had a very large experience, and his conclusions are therefore worthy of consideration. The book is brief, divided into six chapters as follows: 1, What is Inebriety; 2, Pathology; 3, The Causes of Inebricty; 4, The Forms of Inebriety; 5, Treatment; 6, Ether Inebriety, etc., and an Index. Perhaps the best chapter is the one on treatment and this is doubtless the one of most interest to the student of these troubles. The readers of this work should not be misled by the optimism of the author, which at times leads him, we feel, to exaggerations.

The Diseases of China, Including Formosa and Korea. By W. Hamilton Jefferys, M. D., Medical Missionary in China, etc., and James L. Maxwell, M. D., Medical Missionary in Formosa, etc. Illustrated. Price $6. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

A couple of sentences from the authors' preface set forth clearly the nature and scope of this interesting work. "It is necessary to emphasize that this book is not in any sense intended to be a general text-book of medicine, nor even to cover the whole ground of the diseases met with in China . . . . Our aim is to present to medical men working in China, both Chinese and foreigners, a concise account of the special diseases they will meet with in their own practice in this Empire." This is a really valuable work, therefore, for all men intending to be missionaries, and there is also much information in it which is important to students elsewhere. The authors' statements in regard to syphilis and parasyphilitic affections should throw new light on the development of these obscure troubles. There is a picturesqueness about the work which is generally lacking in medical text-books and Drs. Jefferys and Maxwell are to be sincerely congratulated on the success of their task.

Progressive Medicine. Edited by Hobart Amory Hare, M. D., and Leighton F. Appleman, M. D. Vol. IV. December, 1910. (*Philadelphia and New York: Lea & Febiger.*)

A word only is needed to call attention to this last volume of the series which has appeared in the "Diseases of the Digestive Tract and Allied Organs, The Liver, Pancreas and Peritoneum—the Diseases of the Kidneys—Surgery of the Extremities, Shock, Anæsthesia, Infections, Fractures and Dislocations, and Tumors —Genito-urinary Diseases—Practical Therapeutic Referendum." The reviewers are Belfield, Bloodgood, Bradford, Landis and Lavenson, each of whom covers his territory so satisfactorily that no article of real importance on a given subject is overlooked, and there is careful weighing of the merits of each paper referred to.

Physicians Visiting List. (*Philadelphia: P. Blakiston's Son & Co., 1910.*)

Numberless physicians will find this pocket note-book, with its medical tables of incompatabilities, weights and measures, doses, etc., useful, and every physician should carry some such note-book. No one has a perfect memory and doctors should be especially careful to preserve notes and memoranda dealing with their patients. The 60th issue of this Visiting List shows that the publishers have gained a well-earned success with it.

The Care and Training of Children. By Le Grand Kerr, M. D., etc. (*New York and London: Funk & Wagnalls Co., 1910.*)

The author has written other works on babies and children, all marked by careful thought, and good judgment. This small, neatly printed volume is a helpful guide for young parents, and many older ones could also read it with advantage. Dr. Kerr talks simply and pleasantly about The Child's Room, Clothing, Diet, Bathing, Education, Punishment, Government of the Child, Child's Friends and Amusements, and other matters of importance to

the welfare of a child. The question of the correct up-bringing of children is a ever vital one, and this book is sure to lead some mothers and fathers to do better than they would have done without it.

Bismuth Paste in Chronic Suppurations—Its Diagnostic Importance and Therapeutic Values. By Emil G. Beck, M. D. With an introduction by Carl Beck, M. D. And a Chapter on the Application of Bismuth Paste in the Treatment of Chronic Suppuration of the Nasal Accessory Sinuses and the Ear. By Joseph C. Beck, M. D. Illustrated. Price $2.50. (*St. Louis: C. V. Mosby Company, 1910.*)

Through articles in the medical journals Beck's original use of bismuth paste in this form of suppuration has been known for several years, and his practice has been followed with more or less success by many surgeons. At last in book form he presents his experience with this method of cure, and the profession will be grateful to him for it, since this is the first authoritative and full report on this subject which is of real importance in surgery. One of the values of this book is that it is not too long, and the matter is so well presented that its readers can easily read it through. Its essential importance is in making clear to practitioners the real and great values of bismuth when properly used in these surgical conditions.

The Dawn of the Health Age. By Benjamin Moore, M. A., D. Sc., M. R. C. S., L. R. C. P. Price $1.40. (*London: J. & A. Churchill. Philadelphia: P. Blakiston's Son & Co., 1911.*)

Dr. Moore's object in writing this book, is, as explained in the preface, "to demonstrate on clear, broad lines, the necessity for entirely remodelling the present system of medical service, in the interests of the whole community." Much remodelling of medical service is necessary here as well as in England, and those interested in the larger problems of the profession will be glad to read this book, that they may see the difficulties, and study the cure proposed by the author. He suggests that all hospital appointments should be under the control of the State, and all doctors be paid by the State, so that there should be no rivalry amongst them, and so that the State might be better served. To stamp out tuberculosis he thinks the State should have the right to segregate all suffering from this disease until they died or were cured. Such radical measures do not seem feasible at the present moment, but who can foresee what changes will come about sooner or later in society, or what reforms a socialistic government might introduce.

Report of the International Commission on the Control of Bovine Tuberculosis. Reprint from 47th Annual Report of the American Veterinary Medical Association, September, 1910.

The Commission is composed of men well fitted by their knowledge and experience to deal with the problem under consideration, and their report evidences a careful review of the many factors entering into this difficult question. Their recommendations are made under four headings: (1) Education and legislation. (2) Location of tuberculosis. (3) Dissemination. (4) Disposition of tuberculous animals.

The recommendations under the head of education are very wise and practical and may be regarded as the first and most fundamental step in the entire campaign. Without intelligent coöperation on the part of the farmers, dairymen, butchers and consumers, legislation will fail.

The value of the tuberculin test is fairly defined and the recommendations for its use and safeguard from abuse are clearly set forth.

Until more widespread organization occurs—State Livestock Sanitary Boards, or other competent authority for wisely enforcing laws relative to bovine tuberculosis--little can be expected from legislative enactment.

The recommendations of means by which owners of herds can prevent their infection, or eradicate tuberculosis, or build up new herds free from tuberculosis are practical and deserve a more extensive trial than they have yet received in this country.

W. L. Moss.

Remedial Gymnastics for Heart Affections Used at Bad-Nauheim. Being a translation of "Die Gymnastik der Herzleidenden," von Dr. Med. Julius Hofmann und Dr. Med. Ludwig Pöhlman. Berlin und Bad-Nauheim. By John George Garson, M. D. Edin., etc. With fifty-one full-page illustrations and diagrams. Price $2. (*New York: Paul B. Hoeber, 1911.*)

With a few pages to explain the value and proper use of gymnastics in diseases of the heart, supplemented by photographs, with accompanying descriptions of the exercise shown, this book should appeal to many a practitioner, who has not had the chance to learn what gymnastic exercises can be safely practiced by a patient with heart trouble, and how his heart will be strengthened by them. But the physician must be able first to make a careful diagnosis of the condition of the patient, for a hap-hazard treatment of heart disease with gymnastics would quickly prove fatal in many a case. The diagnosis having been made then this work can be safely used, and can be recommended without danger.

Emanuel Swedenborg's Investigations in Natural Science and the Basis for his Statements Concerning the Functions of the Brain. By Martin Ramström. University of Upsala, 1910.

The 200th anniversary of the University of Upsala has inspired an interesting review of the published and unpublished conceptions of one of the most remarkable men of the Swedish nation—Swedberg, later ennobled and renamed Swedenborg. Born in Stockholm January 25, 1688, be obtained his philosophical degree 1709, became assessor extraordinary of the Royal College of Mines 1716, was ennobled 1719, ordinary assessor 1724, retired 1745, and died in London March 29, 1772. A man of extraordinarily wide interests and wide opportunities, he has achievements in mathematics, in geology, neurology, chemistry, physics and cosmology, and finally he threw himself with intense zeal into anatomical and physiological studies which are published as "Œconomia Regni Animalis," dealing mainly with the blood, the brain and the soul. He foreshadowed the theory of epigenesis. His main interest in the brain lies in his emphasis of the "sphærula," or cerebellula of the cerebral cortex (now recognized as the cell-bodies), from which fibers arise and extend to medulla and cord and all parts of the body. The cortex is the seat of the sensorium commune and also of the motility. Each little cell lies in its own cavity and has its own fiber and a certain independence; but they also work together in groups; and he suggests that the relation of the convolutions to the one or the other muscle in the body could only be established on living animals by puncture, section and compression of the convolutions. He also accepted subordinate secondary motor centers for automatic and habitual movements in the medulla and cord. The soul in turn is localized in the cortex and if it were not for the difficulty about immortality he would identify it with the fluidum spirituosum of the cerebellula. "It amounts to the same thing if we see in this fluid the soul itself or only its faculty of imagination and judgment, for the one cannot be thought of without the other." In a manuscript, partly published in London, 1882 and 1887, under the title "The Brain," he extended his work and even developed the fact that in the motor representation in the anterior parts of the brain, the feet depended upon the highest parts, the abdomen and thorax on the middle and the face and head upon the third lobe.

In his historical study, Ramström aims to account for the foundation of Swedenborg's conclusions. The data seem to have

been literary, used with the intuition of a genius, but neither in him nor in his influence on the reader a spur to direct investigation.

Treatises of Fistula in Ano, Hemorrhoids and Clysters. By John *Arderne.* From an Early Fifteenth Century Manuscript Translation. Edited with Introduction, Notes, etc., by D'Arcy Power, F. R. C. S. Eng. Price 15s. (*London: Kegan, Paul, Trench, Trübner & Co., and Henry Frowde, Oxford University Press, 1910.*)

Though the operative material of mediæval surgeons was necessarily quite limited in amount, no one can come away from their writings with anything but respect for the extensive knowledge they managed to accumulate with inadequate clinical methods. This is the feeling which Arderne's work awakens. Its phraseology is charmingly quaint; and it abounds in shrewd, wily advice, and a sly, though none too refined, humor. The author was a "type of surgeon who has happily never been absent from England—an English gentleman as well as a fine surgeon"; and much of what he writes has to do with the ethics of the profession: which is quite intelligible when one remembers the none too savory reputation of the surgeons of the day, and their methods, not always above reproach. He is strong for caution; advises against undertaking a case, except deliberately; always mentions the untoward results that may be expected; and insists on the surgeon having a definite understanding with the patient's relatives—even to an advance-collection of a portion of the fee—before an operation is done. If the emphasis laid on this sort of worldly wisdom seems out of proportion, one has to remember how precarious was the standing of the surgeon in these days; and to recall King John of Bohemia, who sewed up his French leech in a sack and threw him into the Oder because he had not cured his cataract as he had promised.

Arderne advised the operative treatment of fistula and devised needlessly cumbersome instruments for it; but the great advance he made seems to have been in the avoidance of the corrosive and irritating after-treatment used by every one else. Again and again he emphasizes the importance of letting wounds alone.

Hemorrhoids—which, unless they bled too profusely, he regarded as of use in preventing "mania, melancolia, pleuresis, ydropisy, passions of the spleen," etc.—were treated by local applications.

The Treatise of Arderne belongs to the series published by the Early English Text Society; and has been excellently edited by D'Arcy Power. The antiquated spelling, and many of the peculiarities of the original type have been retained. This has enhanced the attractiveness of the book; and though it has made it somewhat more difficult reading, the text has been rendered quite accessible by an excellent running commentary of marginal notes.

The Official Announcement of the University of Vienna about its Post-Graduate Medical Work, published by Urban and Schwarzenberg of Berlin and Vienna, will be sent to anyone on application to Rebman Company, New York, free of charge. This pamphlet is printed in German, but accompanied by an English and French translation, so that no prospective student need have any difficulty in understanding exactly the condition of post-graduate work in that university before going there.

Golden Rules of Ophthalmic Praeticc. By Gustavus Hartridge, F. R. C. S., etc. Golden Rule Series, No. VII. Fifth edition. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1910.*)

That this small work is very popular is shown by the appearance of its fifth edition. This series of "Golden Rules," volumes measuring only 4¼ by 2¾ inches, seems to have had marked success among English practitioners, and there is no doubt that the rules are well chosen, but there is danger that such books, no matter how well prepared, lead to superficiality of work. The practice of medicine cannot be regulated by hard and fast rules, even when "golden."

"Salvarsan" ("606") (Dioxy-Diamido-Arsenobenzol). Its Chemistry, Pharmacy and Therapeutics. By W. Harrison Martindale, Ph. D. Marburg, F. C. S., and W. Wynn Westcott, M. B. Lond., D. P. H. Price $1.50. (*New York: Paul B. Hoeber, 1911.*)

The Treatment of Syphilis by the Ehrlich-Hata Remedy (Dioxydiamido-Arsenobenzol) A Completion of the Published Observations. By Dr. Johannes Bresler. Second edition. Much enlarged, with portraits of Ehrlich and Schaudinn. Translated by Dr. M. D. Eder. With an Abstract of the Most Recent Papers. Price $1. (*New York and London: Rebman Company, 1911.*)

The work by Bresler supplements that of Martindale and Westcott to a certain extent, for even in theirs there is some account of the papers abstracted by him. Both books are useful and arrive at a most opportune moment when "606" is being put on the market. Practitioners must carefully study all the latest information on this subject and we recommend heartily "Salvarsan" in which they will find the proper methods of giving this drug set forth clearly, and its dangers noted. Martindale and Westcott have prepared an excellent manual, containing what is most essential for the instruction of the profession at large on this new remedy.

The Principles of Bacteriology. A Practical Manual for Students and Physicians. By A. C. Abbott, M. D., Professor of Hygiene and Bacteriology in the University of Pennsylvania. Eighth edition. Thoroughly revised. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1909.*)

The 8th edition of this well known book scarcely calls for extended comment. Naturally a large portion of the text is practically unchanged. As the author remarks in the preface: "The advances in bacteriology which have occurred since the issue of the 7th edition have been considerable, but not such as to affect materially the fundamentals essential to the education of the beginner." Parts of the book, however, have been rewritten, notably the chapter on infection and immunity, and the work has been brought up to date in other respects, as far as is compatible with the purpose it is intended to serve; namely. as a manual for students and practitioners of medicine.

A Handbook of the Surgery of Children. By E. Kirmisson, Professor of the University of Paris; Surgeon to the Hospital for Sick Children, etc. Translated by J. Keogh Murphy, M. C. (Cantab.), F. R. C. S., etc. Price $7. (*Henry Frowde, Oxford University Press. Hodder and Stoughton, Warwick Square, E. C., 1910.*)

The author says he has left out all pure theory, history, pathological anatomy and pathogeny in order to insist on the knowledge of symptoms, diagnosis and treatment.

He divides all infantile surgery into two great subjects. Firstly, the study of malformations, and secondly, diseases connected with the locomotor apparatus. To these must be joined certain other affections such as appendicitis, mastoiditis, diseases of the throat, empyema, intussusception and lastly prolapse and polypi of the rectum.

The book is separated into four parts. Part I, 280 pages. Surgical affections of congenital origin which include, Congenital

Affections of the Back, the Head and the Neck; Congenital Malformations of the Trunk; Malformations of the Extremities. Part II, 75 pages. Injuries in Childhood. Part III, 418 pages. Inflammatory Lesions and Disorders of Nutrition, which are divided into Disorders of the Locomotor Apparatus: Affections of Different Regions. Part IV, 30 pages. Neoplasms or Tumors.

The chapter on anesthesia is by Cecil Hughes. He prefers chloroform, either alone or in mixtures, for anesthesia in children. This is interesting as the majority of anesthesias in this country are with ether, which is safer, in most instances.

The translator has used, as far as possible, the author's own words, and his work is nicely done. He has added a few well considered footnotes of his own.

The book is well gotten up and is profusely illustrated.

While some of the authors' ideas are at variance with those generally accepted nevertheless the book accomplishes its purpose, and will be a helpful addition to the other works on the surgery of children which have appeared in the last two years.

J. S. D.

Bier's Textbook of Hyperæmia as Applied in Medicine and Surgery. By Professor Dr. August Bier, of Berlin. Only authorized translation from the sixth German revised edition. By Dr. Gustavus M. Blech, Professor of Clinical Surgery, Illinois Medical College. With thirty-nine illustrations. Price $4. (*New York: Rebman Company.*)

The chapter on the treatment of acute inflammation and suppuration has been changed and enlarged. Chapters on the treatment of keloids, tenosynovitis and diseases of the skin have been inserted. An index has also been added.

The work is well translated and nicely gotten up. There is an extensive bibliography throughout. The author takes up certain criticisms of his methods and demolishes them.

There is no doubt of the efficacy of hyperemia in a number of conditions, and we have all seen good results following its proper use, but the method is hardly a panacea as one might believe after glancing over the volume.

J. S. D.

The Vegetable Proteins. By Thomas B. Osborne, Ph. D., etc. Price $1.20. (*London, New York, Bombay and Calcutta: Longmans, Green & Co., 1909.*)

This little volume of about 100 pages by the well-known authority on vegetable proteins, Thomas B. Osborne, of New Haven, Conn., is one of the Monographs on Bio-chemistry edited by Plimmer and Hopkins. It is a clear, concise, carefully written exposition of the present state of knowledge in this somewhat confusing branch of chemistry. Dr. Osborne has himself been the chief contributor in this field for a number of years, and the book is, therefore, not merely a review of the work done by others, but an expression of his own views. Outside of Osborne's own laboratory comparatively little research on vegetable proteins has been carried out since the investigations of Ritthausen, which were not generally credited immediately after their publication, but which are now abundantly approved largely by the investigations of the author of this book.

The volume is divided into 11 chapters in which the occurrence of proteins in different parts of plants and their general characteristics, the isolation and separation of seed proteins and their reactions in respect to solubility, precipitation, denaturing and hydrolysis are considered with great detail. The classification of vegetable proteins which Dr. Osborne employs is based upon the work of the American committee on nomenclature, but at the same time the author points out that the American and English committees appointed to consider this subject are in practical uniformity in their views.

To the medical man the last chapter of the book in which such subjects as tox-albumens, anaphylaxis, precipitins and agglutinins are considered, is naturally the most interesting. The occurrence among plants of reactions which originally were seen with animal tissues is not without deep significance in view of the fact that many of the diseases in man may be traced to microorganisms belonging to the vegetable kingdoms.

The volume is furnished with a most complete bibliography of over 600 references in accordance with the wishes of the editors that each monograph should furnish a complete list of the papers previously published on the subject of which it treats.

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SIR RICHARD OWEN: HIS LIFE AND WORKS.*

By C. W. G. Rohrer, M. A., M. D., Ph. D., Baltimore.

Doubtless some of you have questioned yourselves concerning the "why and wherefore" for this paper, entitled "Sir Richard Owen: His Life and Works." I wish to give three brief reasons for thus imposing upon your time and good nature.

1. Because of Professor Owen's contributions to medical science.
2. Because of Professor Owen's contributions to the allied sciences. And,
3. For purely sentimental reasons. On Monday, April 4, 1898, when I was a second-year medical student, I attended a Young Men's Christian Association lecture delivered by the late Dr. Daniel C. Gilman, an honored president of this university. In the course of Dr. Gilman's remarks he gave us the following terse bit of advice: "Read biography. Familiarize yourself with the lives of the good and great."

Birth and Parentage.

Richard Owen, the subject of my sketch, was born on Thurnham Street in the town of Lancaster, England, on July 20, 1804. He was the younger son of Richard Owen, formerly of Fulmer Place, Bucks. His grandfather, William Owen, married Elizabeth, daughter of Richard Eskrigge. This Richard Eskrigge was high sheriff of Bucks in 1741, and was the owner of Fulmer Place. In an old family prayer book, dated 1713, with a frontispiece portrait of Queen Anne, and further "adorn'd," as the title-page has it, "with 50 historical cuts," there are the following entries in Richard Eskrigge's handwriting:

Richard Owen, son of William Owen (who was free of the Fishmongers' Company) and of Elizabeth Owen. The said Richard was born in the parish of St. Matthew, Friday Street, December 5, 1754, and baptized the Sunday following. The sponsors were Richard and Elizabeth Eskrigge and Mr. Beresford (Cashier in the Bank of England)."

Then, in Sir Richard Owen's handwriting, a few explanatory remarks are added. He writes:

The above entries are in the handwriting of my great-grandfather, Richard Eskrigge, of Fulmer Place, Fulmer, Bucks, and relate to the birth of his grandson and heir, my father, Richard Owen.

There is also the following entry in the handwriting of Sir Richard Owen's father:

Richard and Catherine Owen were married at Preston, November 8, 1792, by the Rev. H. Shuttleworth.

This latter Richard Owen was Sir Richard Owen's father, and the Catherine Owen mentioned was Sir Richard Owen's mother. Sir Richard Owen's mother was of French extrac-

* Paper read before the Johns Hopkins Hospital Historical Club, January 9, 1911.

tion. She was of a Huguenot family of the name of Parrin, who eame over from Provence at the revocation of the Ediet of Nantes. Her full maiden name was Catherine Longworth Parrin.

Sir Riehard Owen's mother, besides being a woman of great refinement and intelligence, was an accomplished musician. Her father before her had supported himself by the profession of music, and she inherited his talent. In appearanee she was a handsome, Spanish-looking woman, with dark eyes and hair. Owen himself never tired of speaking of his mother's charm of manner, and of all that he owed to her early training and example.

Sir Riehard Owen's father was a complete contrast. Tall, stout and ruddy, his general appearance bore a strong resemblanee to the face and figure popularly supposed to belong to the typical John Bull. Nor was his character unlike —bluff, burly, obstinate, and perhaps not partieularly brilliant, he was yet possessed of sound eomnion sense.

Childhood and Youth.

Sir Richard Owen as a school-boy succeeded admirably with his studies. In 1808, when Owen was but four years of age, his father, a West India merchant, and often absent from home, included the following sentence in a letter to his wife: "I am glad to know James and Richard come on so well with their studies and are so attentive." James was Professor Owen's elder brother.

After the above preparatory instruetion given by an old Quaker lady, Richard Owen, at the mature age of six, was sent to the Lancaster Grammar School to join his elder brother James. Whewell, the famous master of Trinity, who was Owen's fellow-townsman, also received the first rudiments of his education at this school. Another school-fellow who was in the same class as Owen's elder brother was Higgin, late Bishop of Derry.

One of Owen's teachers in the Lancaster Grammar School stigmatized him as "lazy and impudent," and prophesied that he would come to a bad end. This gentleman gave instruction in penmanship. However, in spite of his dismal predictions he managed to teach Owen to write a remarkably clear and neat hand, which hardly varied till within a few years of his death.

"At this period of his life," as Professor Owen's last surviving sister would relate, "Richard was very small and slight and exceedingly mischievous, and he hardly grew at all until he was sixteen."

Owen's family were evidently apprehensive that it would end by his being a "small man." But he soon began to make up for his early want of stature, and when he left the Grammar School he was already a big, awkward lad. At mature manhood Professor Owen's height was six feet in his socks.

At the age of fourteen Richard Owen had given no signs of a taste for the work to which his life was afterwards devoted. Part of a manuscript treatise on "Heraldry" still exists, which he wrote about this time, as well as an elaborately painted eoat of arms of the Owen and Eskrigge family.

Early Education.

Soon after leaving school Riehard Owen was apprenticed to "Leonard Dickson, of Laneaster, Surgeon and Apotheeary," as his indenture dated August 11, 1820, shows. According to the terms of this document Owen was to be provided by his mother with "meat, drink, washing and lodging, and also decent and suitable elothes and wearing apparel," and his master was on his part to teach him the "arts, businesses, professions, and mysteries of a surgeon-apothecary and man midwife, with every eircumstance relating thereto."

Mr. Dickson died two years after, and Richard Owen was "assigned, transferred, and turned over" by the executors to Joseph Seed for the term of five years, the indenture of this transfer bearing the date of June 19, 1822. The following year Mr. Seed aecepted a post as surgeon in the Royal Navy, and Owen was again transferred, by an indenture dated December 13, 1823, to James Stockdale Harrison, "Surgeon and Apotheeary."

There is appended to the indenture to Seed a certificate in Joseph Seed's handwriting, which contains the following paragraph:

> Mr. Richard Owen's general conduct during the time he was with me has my highest commendation, and at all times I shall be happy to bear testimony to his most deserving merit, as well as to his respectability.
>
> (Signed) J. Seed,
> Surgeon Royal Navy.
>
> Lancaster, January 10, 1827.

The terms of Owen's surgical apprentieeship at Lancaster were never carried out to the full. In October, 1824, he matriculated at Edinburgh University. Some of his lecture cards of admission are still preserved. We gather from them that he attended, besides numerous other lectures, the anatomical leetures of Monro (tertius); but as that worthy gentleman was in the habit of lecturing—so Owen had remarked —from the notes used by his grandfather and his father, both of whom had suecessively occupied the chair of anatomy before him, these leetures were found to be neither of particular interest nor yet sufficiently up to date. So Owen was constrained to attend the outside eourse given by Dr. Barclay on practical anatomy, and anatomy and surgery. Though this was an extra which he could ill afford, still he never regretted it, for of all his teachers at Edinburgh it was to Dr. John Barclay that he owed the most. Many times had Owen spoken of the influenee that Dr. John Barclay had on his early career, and the sincere affection with which he inspired him. At this time there were but two leeturers on anatomy in Edinburgh—Dr. Monro and Dr. Barclay. Liston entered the arena as number three.

At the end of April, 1825, Dr. Barclay strongly advised Owen to move to St. Bartholomew's Hospital, London, and study under Abernethy. After some eonsideration, Owen decided to do so, and obtained his college eertificates forthwith, all of which are in existence.

Dr. Barclay (April 25, 1825) speaks of Owen in the following terms in his certificate: "I had much reason to be satisfied with the mode of his attendance, and the manner in which he prosecuted these branches of his medical studies" (anatomy and surgery).

But Dr. Barclay's chief recommendation was a private letter to his friend Abernethy, which he gave to Owen to take to London with him.

Owen was a perfect stranger when he arrived in London. The only connection which he had with his northern friends was Dr. John Barclay's letter of introduction to Dr. Abernethy. This, however, subserved a most useful purpose.

Abernethy had just finished lecturing when Owen arrived at St. Bartholomew's Hospital. He received Owen rather gruffly. Owen presented his letter of introduction from Dr. Barclay. Abernethy read it hurriedly, stuffed it into his pocket and made an appointment with Owen to breakfast with him at eight o'clock the next morning.

When Owen presented himself at Abernethy's residence the next morning he anticipated anything but an agreeable conference with the great physician and surgeon. He found him, to his great surprise, considerably smoothed down and quite pleasant in manner. The result of this meeting was, that Abernethy offered him the post of prosector for his lectures.

To young Owen this was a very desirable position. It possessed several obvious advantages. The prosector was relieved of the necessity of purchasing his own subjects for dissection—no inconsiderable item of expenditure then. This unexpected source of revenue was indeed a saving grace to the young medical student. Owen's father, having suffered severe financial loss, died of a broken heart in 1809, when the boy Richard was but five years old. The mother and six children, two sons and four daughters, were not left penniless, but their means of support were quite meager. For these reasons Richard Owen was early largely thrown upon his own resources.

From such a chief as Abernethy, Owen could not fail to profit. His prosectorship brought with it another decided advantage—the subjects provided for the lectures were in a much sounder and fresher condition, comparatively speaking, than was usually the case in those ever-memorable body-snatching days. To the mind of your humble speaker, this so-called "body-snatching" epoch forms one of the most interesting periods in the whole history of medicine. The wonderful story of John Hunter's persevering efforts to obtain the body of O'Brien, the Irish giant, who died in 1783, should be read by every medical student.

As a rule, Owen fared well at the hands of his professor, Dr. Abernethy; but on one occasion he provoked Abernethy to anger. The lecture was on the human kidney, which Owen had duly prepared. But, unfortunately, in the process of preparation the adrenal gland became detached, owing, most likely, to its not being quite so fresh as it might have been, and, in a great hurry, the prosector carefully fixed it on again—but to the wrong end of the kidney. Abernethy's explanations were somewhat far advanced before he found this out, and not looking very closely at the specimen he held in his hand, he was elaborately describing its structure, as if it had been a normal kidney. When he discovered the error committed, he did not let the occasion pass without bestowing a few flowers of speech upon his young friend.

Professional Career.

On August 18, 1826, Owen obtained his membership of the Royal College of Surgeons. He had then just entered his twenty-third year. His diploma is signed by twelve great men, the three most familiar ones being John Abernethy, Astley Cooper and Everard Home (John Hunter's brother-in-law).

Owen set up as a medical practitioner at 11 Cook's Court, Carey Street, Lincoln's Inn Fields, and gradually secured a small practice among the lawyers. He also diligently visited the poorer classes of the neighborhood.

John Hunter having died in 1793, his rare, valuable and unusually complete collections numbering 3970 specimens were purchased by the government for the sum of $75,000 and given into the custody of the Royal College of Surgeons. Down to this time (1826) these Hunterian collections had been sadly neglected. For twenty-five years Sir Everard Home was "going to" prepare a descriptive catalogue of the collections which had been transferred by the government from John Hunter's temporary museum in Castle Street to the Royal College of Surgeons.

Owen's peculiar ability as a dissector had not escaped the eagle eye of Abernethy, then president of the Royal College of Surgeons. Abernethy, who was much concerned at the neglect of the collections formed by John Hunter, which had recently been purchased by the government and handed over to the care of the college, insisted on his old pupil, Richard Owen, undertaking their arrangement. As Abernethy said: "The collection was located near his (Owen's) private residence; he could devote his leisure hours to the work; there was no one else equally qualified to do so." Owen undertook the task, and was thus associated with William Clift, at that time conservator of the college museum, and who subsequently became his father-in-law.

In the year 1828 Owen was appointed lecturer on comparative anatomy at St. Bartholomew's Hospital, an appointment which was the starting point of his career as a lecturer. Early in 1834 Owen was appointed professor of comparative anatomy at St. Bartholomew's.

In April, 1836, Owen was appointed Hunterian professor at the Royal College of Surgeons. To the last days of his life he constantly referred to the gratification which this appointment gave him. As Hunterian professor it was Owen's special duty to deliver twenty-four annual lectures, as illustrative of Hunter's collections.

On the retirement of Sir Charles Bell, of Bell's paralysis fame, from the professorship of anatomy and physiology in the Royal College of Surgeons, in the early part of 1837, Owen was elected to the vacant chair. Owen's full title then

became "Hunterian Professor and Professor of Anatomy and Physiology in the Royal College of Surgeons."

Owen now (in 1837) began gradually to relinquish his medical practice in order to devote the whole of his time to scientific research. He had been a practitioner of medicine and surgery for eleven years.

On May 2, 1837, at 5 o'clock p. m., Professor Owen delivered his first Hunterian lecture. The subject of this course of lectures was the microscopical structure and nature of the teeth.

On June 19, 1837, Owen was elected Fullerian professor of comparative anatomy and physiology to the Royal Institution. This professorship Owen was obliged to decline.

Owen filled the position of Hunterian professor of anatomy and physiology at the Royal College of Surgeons for a period of twenty years (1836 to 1856). On May 26, 1856, Owen was appointed superintendent of the natural history department of the British Museum, at a salary of 800 pounds (about $4000) a year. This appointment was originally suggested by Lord Macaulay. The office of superintendent was generally understood to have been created expressly for Owen.

Long after Macaulay had abandoned all other public business, he continued to occupy himself in the administration of the British Museum. In February, 1856, he wrote to Lord Lansdowne with the view of securing that old friend's potent influence in favor of an arrangement by which Professor Owen might be placed in a position worthy of his reputation and of his services. The following is an extract from Macaulay's letter to Lord Lansdowne, in which he proposes that Professor Owen should be constituted superintendent of the whole department of natural history, including geology, zoölogy, botany and mineralogy.

Macaulay writes:

> I cannot but think that this arrangement would be beneficial in the highest degree to the Museum. I am sure it would be popular. I must add that I am extremely desirous that something should be done for Owen. I hardly know him to speak to. His pursuits are not mine; but his fame is spread over Europe. He is an honour to our country, and it is painful to me to think that a man of his merit should be approaching old age amidst anxieties and distresses. He told me that eight hundred a year (meaning 800 pounds a year) without a house in the Museum, would be opulence to him. He did not, he said, even wish for more. He seems to me to be a case for public patronage. Such patronage is not needed by eminent literary men or artists. A poet, a novelist, an historian, a painter, a sculptor, who stood in his own line as high as Owen stands among men of science, could never be in want except by his own fault. But the greatest natural philosopher may starve while his countrymen are boasting of his discoveries, and while foreign Academies are begging for the honor of being allowed to add his name to their list.

Professor Owen entered upon the duties of his new office, that of superintendent of the natural history department of the British Museum, on June 8, 1856. This position Professor Owen held for twenty-eight years, or until he had almost reached the eightieth year of his age.

The superintendency gave Professor Owen an opportunity to do a little outside work. In 1857 Professor Owen was appointed lecturer on palæontology at the Royal School of Mines. His first lecture was given on February 26, at the Museum of Practical Geology. Amongst the audience, as an entry in the diary shows, were many old friends: Dr. Livingstone, Frank Buckland, the Duke of Argyll, with his sons, Sir Charles Lyell and Sir Roderick Murchison.

Towards the end of 1857 Owen was offered and accepted an appointment which some years previously, while at the Royal College of Surgeons he was obliged to decline; it was the Fullerian professorship of physiology at the Royal Institution of Great Britain.

Private Life.

Professor Owen was one of the most affable of men. His home-life was ideal. In scientific circles he was universally loved and respected. Even those whose views ran counter to his own always dealt with him with the highest consideration. His earnestness of purpose, his sincerity and frankness, were marked traits of his character.

On July 20, 1835, Professor Owen's thirty-first birthday, the event took place to which he had so long looked forward, namely, his marriage to Miss Caroline Clift. Professor Owen had been engaged to Miss Clift for eight years. It was a very quiet wedding, and is thus described in Miss Clift's diary:

> July 20.—Richard Owen and I, my father and Harriet Sheppard, were in the new St. Pancras Church, Euston Square, by half-past eight o'clock. The Rev. Mr. Laing came immediately after we got into the vestry, and, Caroline Clift having been lost on the road, Mrs. Richard Owen returned to breakfast at No. 1. Euston Grove; after which my husband, my mother and I set off to Oxford.

This union was blessed with one child, William Owen, born October 6, 1837. On October 6, Professor Owen writes in his wife's diary:

> At a quarter-past nine William Owen was born.

The next day there is the entry:

> Papa's joy a little damped by excruciating toothache. Mother and child as well as possible.

About a month afterwards Mrs. Owen begins the diary again. The diaries of Mrs. Owen, began about the year 1827, are now kept almost without a break up to 1873, the year of her death, thus covering a period of at least forty-six years. Many of the scenes and incidents in Professor Owen's life, which I have incorporated in this paper, have been taken from Mrs. Owen's interesting diary.

Mrs. Owen died May 7, 1873, and by her death Professor Owen lost one who had been his fitting helpmate for nearly forty years, and who had, in her younger days especially, assisted his work in no small degree by her acute powers of observation and by her artistic skill.

Contributions to Medical Science.

Owen's most important contribution to medical science is his discovery of the *Trichina spiralis,* a small nematoid worm which harbors in striated muscle and causes the disease known

as trichinosis. This important miscroscopic discovery was made by Owen in the autumn of 1834. At first it seemed merely a curiosity of science. Mr. Wormald, demonstrator of anatomy at St. Bartholomew's Hospital, sent Professor Owen a piece of human muscle accompanied by the following letter:

Dear Owen.—I send you some sort of organised beings, as I believe, which occupy the muscles of a subject now under dissection at St. Bartholomew's Hospital, and as I know you are a keen hand for parasitical things from crabs downwards, I send the enclosed for your inspection.

Ever yours sincerely,

Tho. Wormald.

Upon examining this piece of muscle, Owen discovered a new entozoon, the *Trichina spiralis*. Owen's nomenclature has been slightly changed, and in your recent text-books on pathology you will find this parasite spoken of as the *Trichinella spiralis*. Owen's paper, entitled "Description of a Microscopic Entozoon infesting the Muscles of the Human Body," appeared in the *Proceedings of the Zoölogical Society*, Vol. III, 1835.

This minute worm is not limited in its distribution to the muscles of men, but when in the human body not unfrequently causes death. It is well known as producing the epidemic trichinosis, which formerly made its appearance chiefly in Germany, or in such places where diseased pork or partially cooked ham is consumed. Cobbold, in his masterly treatise on parasites, appends a list of thirty-three epidemics of trichinosis observed in Germany during the first six years immediately following the announcement of Professor Owen's discovery of the *Trichina spiralis*.

The *Trichina spiralis* figures conspicuously in Professor Joseph Leidy's excellent monograph, "Flora and Fauna in Living Animals." Dr. Leidy lays especial stress upon the fact that the inhabitants of the United States are less infected with entozoa than the inhabitants of other countries.

Before leaving this important subject it is intensely interesting to note that the medical student who was making the dissection at St. Bartholomew's was Mr. Paget, who afterwards became the renowned Sir James Paget.

Owen was the last great exponent of the so-called "Vertebrate Theory of the Skull." This theory originated in the fertile brain of the German poet Goethe, in the year 1790; it was greatly elaborated in 1807 by Lorenz Oken, a German anatomist; and further developed and most ably championed by Professor Owen about the middle of the nineteenth century. Professor Owen's views are embodied in his "Report on the Archetype and Homologies of the Vertebrate Skeleton," published in 1846.

The vertebral theory of the skull is based upon the hypothesis that the vertebrate skull consists of four modified or expanded vertebræ—in other words, that the skull is the highly differentiated anterior end of the backbone.

While Owen's classic anatomy was faultless, many of his conclusions were subsequently proven by Huxley to be untenable. These were Huxley's words:

> The spinal column and the skull start from the same primitive condition, whence they immediately begin to diverge.
>
> It may be true to say that there is a primitive identity of structure between the spinal or vertebral column and the skull; but it is no more true that the adult skull is a modified vertebral column than it would be to affirm that the vertebral column is a modified skull.

Professor Owen conferred an inestimable boon upon medical science by editing two octavo volumes of John Hunter's manuscripts. These two volumes of Hunter's unpublished manuscripts, edited by Owen, appeared in 1860, and are entitled "John Hunter's Essays and MSS." These volumes contain essays on natural history, psychology and kindred topics.

Professor Owen was one of the pioneers in public health work and in sanitation. He was chairman of the original Health of Towns' Commission. Sir Henry Littlejohn, the man who made the first sanitary survey of the city of London, mentioned by Dr. Osler in his recent magazine article entitled "Man's Redemption of Man," served with Professor Owen on this commission.

Professor Owen was also a member of the Commission of Sewers and of the Royal Commission on Smithfield Market and the Meat Supply of London.

Contributions to Comparative Anatomy and Physiology.

Owen's contributions to comparative anatomy represent his most exhaustive work. These are largely embodied in his three-volume work, "On the Anatomy and Physiology of Vertebrates," and his one-volume work, "On the Anatomy and Physiology of Invertebrates." Owen was the leading anatomist of the age, and the leading vertebrate anatomist of all time.

An observation which Owen made on the generative organs in the muridæ or mouse and rat family is of interest. This was mentioned in his Hunterian lectures for 1840. The subject of the lectures for this year was "The Comparative Anatomy of the Generative Organs and the Development of the Ovum and Fœtus in the Different Classes of Animals." In these lectures Professor Owen describes for the first time, as separate and distinct glands, the "small glands with a granulated exterior" situated adjacent to the seminal vesicles in the rat and mouse. Previous investigators had described these glandular structures as part of the prostate gland.

Owen also rendered great service to comparative anatomy by pointing out the distinction between homology or structural resemblance and analogy or functional resemblance.

Contributions to Zoölogy.

Owen's contributions to zoölogical literature are almost as innumerable as the sands of the sea. His first zoölogical paper, written in 1830, was "On the Anatomy of the Ourang-outang." In 1832 Owen published his "Memoir on the Pearly Nautilus," the description of which seemed to have given his mind a bent in a definite direction. This was Owen's first work which attracted the attention of scientific men. In the same year Owen published a paper "On the

Mammary Glands of the *Ornithorhynchus paradoxus,*" and another "On the Generation of Marsupial Animals." In 1863 Owen published his "Memoir on the Aye-Aye."

Contributions to Palæontology.

Owen was the first to identify the mammoth, an extinct hairy elephant, and assign it to its proper place in the zoölogical world. Owen was also the first to properly describe the *Archæopteryx,* an extinct bird possessing reptilian characters and supposed to be the transition link between reptiles and birds. The *Megatherium americanum,* an extinct ground-sloth from South America, was the subject of considerable controversy until the appearance of Owen's memoir.

Owen's most notable contributions to palæontology are contained in his monograph on the "Extinct Wingless Birds of New Zealand." Herein Owen describes with characteristic clearness and thoroughness the apteryx, the dinornis, and the notornis, all extinct birds of New Zealand; and in an appendix he describes the extinct dodo of Mauritius, the garfowl of Newfoundland, and the solitaire of Rodriguez.

Professor Owen described six distinct species of the genus dinornis, ascending respectively from the size of the great bustard to that of the dodo, of the emu and of the ostrich, and finally attaining a stature far surpassing three of the once-deemed most gigantic of birds. This latter is the *Dinornis maximus,* or great moa, a large struthious bird "of a heavier and more sluggish species than the ostrich." Its greatest height, as determined by Professor Owen, was probably sixteen feet.

Miscellaneous Contributions.

Professor Owen was the most sought-after man in scientific England. He played a considerable rôle in the discovery of the remains of John Hunter, and in their removal from the vaults beneath St. Martin's Church to Westminster Abbey. These events transpired early in 1859, or nearly sixty-six years after John Hunter's death.

All through Owen's life he was regarded as legitimate prey to the numerous inquirers as to the nature and habits of such fabulous monsters as the cockatrice, the phœnix and the bunyip. Even the question of the existence of a sea-serpent was referred to Owen. In 1848-1849 this "Great Sea-serpent" was alleged to have been seen no less than 187 times. The officers and crew of H. M. S. *Dædalus* also gave a description of this sea-monster. In a letter to the Prince Consort, Professor Owen states his opinion that the "animal" seen from the deck of the *Dædalus* was the head and track of a great seal, or sea-lion. About this time there was another sea-serpent seen, of which the particulars were sent to Owen by the Duke of Northumberland. This Owen demonstrated to be the ribbon-fish from the drawing which was sent. *Punch* soon had a parody on the subject, modeled after the famous Mother Goose rhyme, "Who Killed Cock Robin?" *Punch's* lines began:

"Who killed the sea-serpent?"

"'I,' said Professor Owen."

"Scotched, not killed," was Owen's comment on this.

Owen attempted a classification of animals, based on the nervous system. He also founded the science of "Odontography," or the natural history of teeth.

Even obstetrics was not neglected, because in 1842 Owen wrote a paper entitled "Notes on the Birth of the Giraffe at the Zoölogical Society's Gardens, and description of the fetal membranes, and of some of the natural and morbid appearances observed in the dissection of the young animal."

Summary of Life Work.

Professor Owen's active working life covered the phenomenal period of sixty-five years. His first two papers were on pathological subjects, and were read before the Abernethian Society in 1826: one "On Encysted Calculus of the Urinary Bladder," and the other "A Case of Gluteal Aneurism with Ligature of the Internal Iliac." Owen's first surgical paper was published in 1830. Its subject was "An Account of the Parts concerned in the Aneurism for the Cure of which Dr. Stevens tied the Internal Iliac Artery at Santa Cruz in the Year 1812." Owen's last paper was written in 1889, when its venerable author was eighty-five years of age. It was entitled "A Monograph on the British Fossil Cetacea from the Red Crag."

Owen's published works number 642. These embrace books and monographs in every department of natural history—zoölogy, comparative anatomy, geology, botany, palæontology, anatomy, physiology, geography, chemistry and public health. Owen was one of the earliest workers with the microscope, and a founder and charter member of the Royal Microscopical Society.

Owen received inspiration from the great Cuvier, whom he met in 1831. Owen was called "the British Cuvier."

Owen manifested a great love of chess, of music and of gardening. He was an accomplished 'cellist.

The story of Owen's life has been admirably written by his grandson, the Rev. Richard Owen, M. A. It comprises two volumes. The data contained therein have been largely gleaned from about 1200 of his own letters, written chiefly to his wife and sisters, and from more than 15,000 letters which have been preserved from the voluminous correspondence which Professor Owen received during his long life.

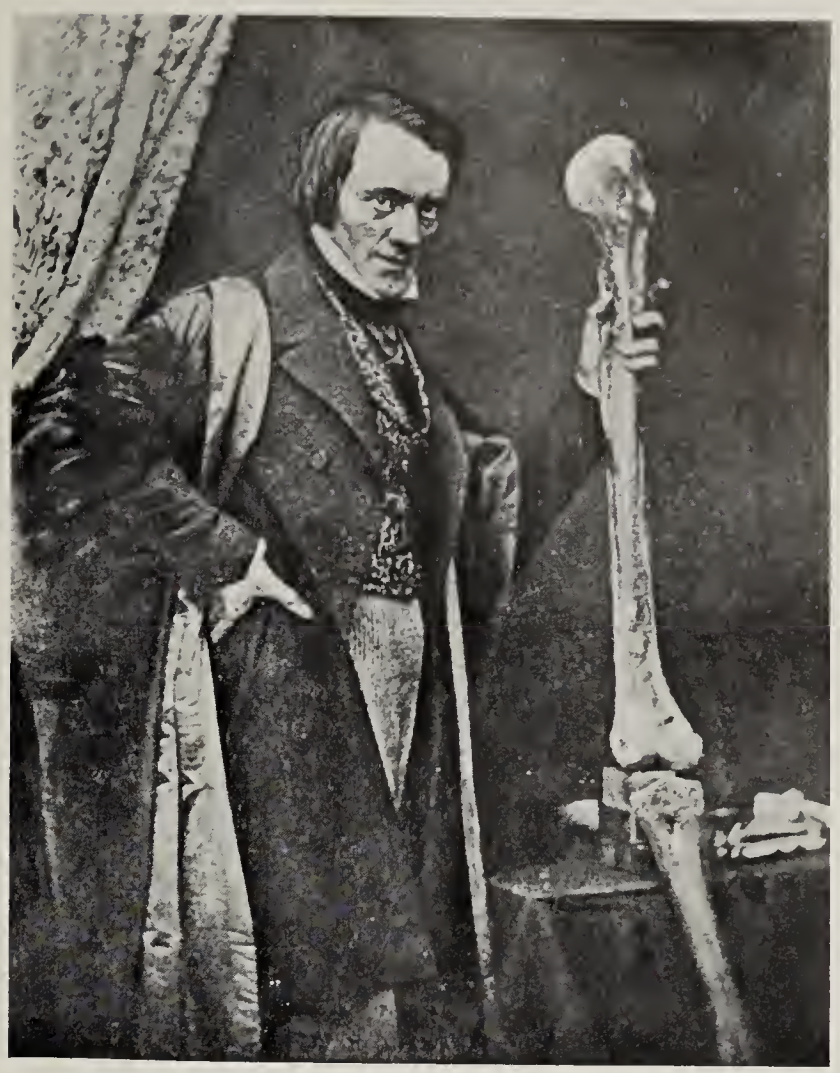
Degrees and Honors.

Professor Owen received four honorary degrees, including D. C. L. from Oxford and LL. D. from Cambridge. He was awarded fourteen medals and was a member of eighty-three learned and scientific societies. These include the Royal Society, of which he was elected Fellow in 1834, and the Linnæan Society.

Owen and Evolution.

Professor Owen, being of deep religious convictions, was a sworn foe of evolution. Owen's works teem with references to the "Divine plan" and the "will of the Creator." But

PROFESSOR OWEN AT THE AGE OF 22 YEARS.



PROFESSOR OWEN IN HIS PRIME—AGED 42 YEARS—AS HE LECTURED. HE HOLDS A BONE OF THE DINORNIS MAXIMUS.

PROFESSOR OWEN—AGED 73 YEARS—AND THE SKELETON OF DINORNIS MAXIMUS.

PROFESSOR OWEN—AGED 85 YEARS—AND HIS GRAND-DAUGHTER.

the crisis came in 1860, when the British Association for the Advancement of Science met in Oxford, England. That this battle for evolution should take place at this time was a foregone conclusion.

But only one man in the whole world had the courage to openly oppose Professor Owen's views or dissent from his opinions. This was a rising young anatomist twenty-one years Professor Owen's junior. It was none other than that great master-mind of the nineteenth century, namely, Thomas Henry Huxley. Everybody knows who Huxley was. Huxley's name is inseparably blended with the early history of *this* great institution of learning; because it was Huxley's most famous pupil, Dr. H. Newell Martin, who organized the biological department in this university.

Huxley plead eloquently for the cause of evolution. Owen, representing scientific England, and Bishop Wilberforce, representing the church and the populace, as eloquently opposed it. Bishop Wilberforce, in the course of his remarks, turned to Huxley and asked him if it was on his grandfather's side or on his grandmother's side that he was related to an ape.

When Bishop Wilberforce had ended his speech, Huxley arose to his feet, and in his usual calm but earnest demeanor made the following reply, which has become historical:

"I asserted, and I repeat, that a man has no reason to be ashamed of having an ape for his grandfather. If there were an ancestor whom I should feel shame in recalling, it would be a *man*, a man of restless and versatile intellect, who, not content with an equivocal success in his own sphere of activity, plunges into scientific questions with which he has no real acquaintance, only to obscure them by an aimless rhetoric, and distract the attention of his hearers from the real point at issue by eloquent digressions, and skilled appeals to religious prejudice.

However, later in life Owen's heart softened toward evolution and evolutionists. Shortly after Louis Agassiz's death, which occurred December 14, 1873, Professor W. J. Stillman of this country visited London and interviewed Professor Owen. Professor Owen spoke feelingly of Agassiz's death, and lamented the fact that our great naturalist had held out so obstinately against evolution. Professor Owen's words were: "If I could have had half-an-hour's conversation with Agassiz, I believe I could have convinced him of the truth of evolution."

After Owen's death in 1892, Huxley wrote a meritorious essay on "Owen's Position in the History of Anatomical Science." It forms the closing chapter in Vol. II, "Life of Owen."

Closing Years.

On January 5, 1884, Professor Owen was knighted, and henceforth we shall speak of him as Sir Richard Owen.

Sir Richard Owen's last days were spent at Sheen Lodge, the beautiful home in the suburbs of London, presented to him by Her Majesty Queen Victoria, in recognition of his services. Sir Richard Owen enjoyed reasonably good health, notwithstanding his excessive mental application. For twenty years he had suffered with chronic bronchitis. Early in 1890 he had a stroke of paralysis, from which he never entirely recovered. But he rallied from it in marvellous way. From this date on, his hearing became visibly affected.

On August 30, 1892, his old friend, Sir James Paget paid him a visit, and tried to converse with him; but Sir Richard, owing to his great prostration, was unable to sustain the effort long. In reply to the repeated inquiries of Dr. Palmer, his physician, Sir Richard invariably answered: "I feel no pain at all, but I have no desire to rise from this bed."

Towards the end of November Sir Richard grew gradually weaker, and began to take less and less nourishment. From the first week of December he never showed the slightest disposition to rally. On December 16 he ceased to recognize those who were standing around him. His death occurred a little before three o'clock on Sunday morning, December 18, 1892.

Sir Richard Owen's death was not due to any definite disease, but to a gradual decadence of all the vital functions. His days had been bounteously prolonged. He was in his eighty-ninth year.

Sheen Lodge, Richmond Park.

The news of Sir Richard Owen's death, like that of Agassiz and of Darwin, created widespread regret throughout the civilized world. The people of all nations, regardless of race or creed, realized that a great figure, not only of the age but of the century, had passed away. Indeed, the world was made poorer by Sir Richard Owen's death, because it lost an untiring scientific worker and a most genial, kind-hearted man.

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A FLORENTINE ANATOMIST.*

By Pearce Bailey, M. D., New York.

It was the peculiar good fortune of Leonardo da Vinci to be sought after and applauded during his life and after it to attain what he thought most worth having, permanent fame. Few men whose names have grown greater with sueceeding centuries have had such praise from their contemporaries. He was the divine genius, the second Appeles, the man who could do anything. Kings and Popes sought him for his personal charm quite as much as for his construetive genius. Francis I told Cellini that no mortal had ever known as much as Leonardo knew, not only in the arts but in everything else. "Naturc had so endowed him," wrote his contemporary biographer, Vasari, "that whenever he put forth thought, will and effort he showed such divine achievement that no one has ever equalled him in readiness, aetivity, quality of product, amiability and graee."

It is not necessary to define the plaee posterity has accorded him in the art which is his chief glory. But Stevenson gracefully vouehes for his personal qualities by counting him one of the two men he ever knew or heard of worthy of a woman's falling in love with; and as the beginnings of seience are day by day being unearthed from old manuscripts, almost as many champions are coming forward now to prove him a pioneer genius as there were then who praised and loved him during his life. Great as are his works of art, the most impressive legacy he left are the evidenees of the universality of his genius.

Philosophe, physicien
Rimeur, bretteur musicien
Et voyageur aerien.

He was all that, but far more. He caught from the blue ideas that had oecurred to no one before, and now are everybody's. He made definite impressions on geology, astronomy, engineering, mechanics, botany, zoölogy, physiology, anatomy. He made no great discoveries. But he foreshadowed all discovery from the theory of cosmic unity to the rural free delivery and the lighter than air machines. He is to be judged by his insight and the breadth of his eoneeptions rather than by his finished products. What he did produce was of such a high degree of exeellence that it is impossible to imagine his doing anything badly.

He had the will to attaek, without whieh no one can be first. In his note-books may be found frequent phillipies against alchemists, necromancers, astrologists and physicians, all of whom, in his day, were opposed to the scientifie idea. A thinker who ean twist a horseshoe with his hands as though it were lead is rarely one to keep his views to himself; and we may think of him as a noble figure with a long beard who wore a red cloak whieh reaehed to his knees; one who defied the fashions, a militant missionary of freedom of thought and progress. Leonardo's love of nature and his profession of sculptor and painter early led him to a study of animal structure. He made notes for a book on how birds fly, and for another on the anatomy of the horse. And with the help of chanee association or his policy of thoroughness, he beeame the first to know how the parts of a man are welded together to make him a mechanieal unit.

One cannot appreciate what this meant in originality and daring without first knowing how little medicine was developed before the Renaissance. If we look back to the early growth of anatomy as an exact and special study, three landmarks stand out elearly between the misty beginnings and the time, in the third century, A. D., when rational knowledge, held in the bosom of the church, went to its long sleep.

These landmarks are Greece with Hippocrates towering over everything, Alexandria with its famous school, and Rome in the time of Marcus Aurelius, when Galen established anatomical teachings which were to be blindly followed for a thousand years.

Hippocrates (d. 380 B. C.) did little more for anatomy than to crystallize the vague eonceptions of his predecessors, none of which were based on human dissections. The laws of Greece required prompt burial of the dead, and that the buried dead be left to sleep in peace. The few anatomical faets, therefore, whieh Greek medicine separated from myth and tradition were gleaned by sueh disclosures of anatomical strueture as were made by the wounds and injuries of war, by unburied bodies which had been separated into their integral parts by the elements, and by sacrificial animals. As a result, the anatomy of the times boasted few proved facts. It was a mixture of symbolism, conjecture and philosophical speculation, too uncertain for rational medicine to build on.

Eight years after the death of Hippocrates, a great change in methods and results was worked at Alexandria. In this famous cosmopolitan eenter of learning, the home of Theoerates, of Euelid and Archimedes, light was thrown on intimate human strueture for the first time. It was made possible by the genius of the Ptolomies. These rulers not only permitted dissection but encouraged it, and in order to remove the odium which had hitherto attached to the deseeration of the human temple, used the scalpel themselves oceasionally.

The school flourished for three hundred years and lived a thousand. But the conquest by Rome brought Roman customs and traditions. With the fall of the Ptolomies, at about the beginning of the Christian era, dissection again fell into discredit and disuse; and the burning of the library was a blow to the intellectual supremacy of Alexandria from whieh it never recovered. Anatomy, however, again saw the sun in Galen (200 A. D.). This man, perhaps the most virile figure in the history of medicine, worked with untiring industry, practiced, traveled, wrote and initiated many original methods of experiment. His eareer was like that of many a Mes-

* Paper read before the Johns Hopkins Hospital Historical Society, October 24, 1910.

siah. Hated by his contemporaries, his teachings and his personality survived his mortal death for many centuries. The activity of his scalpel was limited to animals. His works, which made no mention of human dissection, became weapons of the church. They served as means of curbing the restless inquiry of science, as did the monastic interpretations of the Scriptures in suppressing those wishing to go deeper into the question of man's spiritual welfare. When, in the beginning of the Renaissance, earnest truth seekers, no longer content with the time-worn and erroneous teachings, began to clamor for rational means of renewing and extending anatomical knowledge, the church would answer: "Go to your Galen; he has written truly and all you need to know." Even after human dissections had begun to show how widely Galen's anatomy of animals differed from human anatomy, new prophets, opponents of progress, would arise, who preached against the innovations and upheld the thousand-year-old errors. The cry "back to Galen" was heard as late as the time of Sylvius in 1550.

Galen was a Greek and wrote in his native language. The Arabians were the first to take over and elaborate his writings in their own language. From the Arabic translations they were retranslated into Latin, in which form, garbled and mutilated, they first became accessible to Italian students. They were widely copied in the eleventh and twelfth centuries. Perhaps too wide circulation was the cause of their downfall. At any rate, in the thirteenth or fourteenth century, human anatomy began to be heard of again for the first time since the Alexandrine days. The school of Salerno ordered dissections in the last half of the thirtenth century, and in 1308 the major council of Venice ordered the medical faculty to make a few autopsies every year. But the name above all others associated with the new movement was Mondinus, the little Raimondo, as he was affectionately called, who, as professor or reader of medicine in the University of Bologna, performed his first human dissection in 1315. He could not push his studies far, but his 44-page compendium, which was first copied in MSS., and later printed in many editions, was widely used by the medical schools of Italy and Germany for 300 years. Mondinus made no material advance on Galen's teachings. Many of them he took over bodily without knowing that it was animal and not human anatomy he was teaching.

He heralded the science he could not found. Raising his voice against traditional authority, as he did in his preface, when he said, "non observans stilum altum sed secundum manualem operationum," he stands the John the Baptist of anatomy. The fruits of his example were slow in ripening. The prejudice against mutilation of the human body for any purpose died hard. The rights of the dead were held sacred, as the soul, even of executed criminals, was supposed to be buried with the body. Anatomists, therefore, pursued their studies in the face of viligant opposition, and found themselves becoming midnight marauders.

It was probably more to stop grave robbing than to further the study of anatomy that in 1405 the University of Bologna publicly authorized students of the third year to witness two demonstrations. Both students and masters alike were forbidden to dissect without permission. In 1442 another decree provided the rector of the university with two bodies a year, but no bodies of any one dying nearer than thirty miles of Bologna. So that in the middle of the fifteenth century, when Leonardo da Vinci was born, in the most celebrated university in Europe, it was practically impossible for students to learn how the machine they were to care for was put together. They were not permitted to dissect, they had no books, and such anatomical drawings as were in existence were of no more use than the title page of our *Farmers' Almanac.* This was all changed by Vesalius of Brussels. His treatise on anatomy, *de Fabrica humani corporis,* which Dr. Osler, in the copy of the original edition he presented to the New York Academy of Medicine, calls "the greatest medical work ever printed, the one from which modern medicine dates its beginnings," has for all time crowned Vesalius as the founder of anatomy.

But between the prophecy of Mondinus and the achievement of Vesalius came a man who cannot be overlooked in the history of anatomy, though most of such histories overlook him. A man who inaugurated modern anatomical methods; who studied voraciously, saw keenly and drew with matchless skill what his scalpel brought in sight. This was a man who could give only a small fraction of his time to anatomy, Leonardo da Vinci. Vesalius' book was published in 1543. The great Italian's notes and drawings, made not later than 1510, lay unknown for centuries.

He did his work in Florence and Rome, but probably most of it in Milan. In 1842 he left Florence for the Lombardy capital either to contribute to the gaiety of the court with his famous rhymes and allegories, or to construct the Sforza equestrian statue, or to play on the horse's head-shaped silver lute he had made himself. There, although occupied with the canalization of the rivers and with painting The Last Supper, he found time to carry on dissections. Perhaps he owed his opportunities for the latter to de la Torre, the professor of anatomy at the near-by University of Pavia; perhaps the opportunity came to him by reason of his popularity and charm of manner. "He was so godlike and of such power of persuasion," writes Vasari, "his reason and memory aided him to such a degree, and he could make his views so clear by means of his drawings, that he could convince and confound the most obstinate with his proofs and conclusions." To such a personality all doors fly open and much is forgiven. By virtue of it access to anatomical material was doubtless easier to him than to others, and it is not difficult to believe that many an indulgence was accorded the versatile artist who persisted in pursuing studies in defiance of the sentiments of the times. That he made many dissections is proved by the work he left. Somewhere in the note-books he gives the number as ten. But de Beatis, writing of him when he was an old man living at Amboise under the protection of Francis I, says: "This gentleman has written of anatomy with such wealth of detail, illustrating by his art both limbs and muscles, nerves, veins and ligaments of the inward parts, and of all

that may be demonstrated in the bodies of men and women, in a way that has never been equalled by anyone else. And this we have seen with our own eyes, and he has also told us that he has dissected more than thirty bodies of men and women of different ages."

Leonardo pushed his investigations far beyond the necessities of art: to depict beauty did not satisfy his inquiring mind; he must unravel the very secrets of her being. He sawed the bones lengthwise, to see their internal structure; he sawed the skull in various directions, and was the first to discover the cavities in its walls; he cut through the vertebræ and showed the spinal cord, the link between the brain and the nerves. His restless scalpel exposed the hidden and inaccessible parts and organs of the body. His methods of work were the technical methods of an anatomist, not those of an artist studying anatomy for the benefit of his art. He prepared the vessels for dissection by injection and used a variety of instruments. In the few anatomical sketches left by Raphael and Michael Angelo, the evidences of personal and skilful dissection, unmistakable in all of Leonardo's work, are entirely lacking. They studied anatomy as did the Greeks; Leonardo studied it as does every medical student to-day. He made his drawings of the dissections on loose leaves, on the margins of which he wrote (left-handed) explanations of the drawings, together with notes and suggestions of various kinds. He quotes Galen and Avicenna and proves Mondinus wrong; he tells how many dissections of each part are necessary for proper description, draws diagrams for mannikins arranged with strings, for a proper understanding of the action of the muscles, makes observations on various scientific and philosophical subjects.

Leonardo bequeathed his anatomical note-books to his friend Melzi, who took them with him to Milan. They later had a checkered career, some were lost and some scattered, the largest collection being that at Windsor, which has recently been reproduced in Paris and Turin.

The note-books as we find them are much the same as an anatomist, preparing a book, might draft to-day. The drawings are not arranged in order and the notes are entirely insufficient to serve as a text. But it was Leonardo's intention to write a treatise on anatomy in one hundred and twenty volumes—and the note-books were without doubt the foundation of this project. He prized illustration in everything, and the drawings were the permanent part of the work. This treatise was never finished: perhaps it was never systematically begun. "It is neither avarice nor negligence that has hindered me," he wrote, "but lack of time." So in anatomy, as in almost everything else he did, we are losers in that he did not go further. He left fewer finished works than any other great artist of the Renaissance. But the wonder is that he finished anything. He set himself the highest standards of perfection in execution. And everything he touched aroused in him a seething mass of ideas, speculations and insistent thoughts, which are too often the foes of constructive effort. The world for him was a circus with a hundred rings. He must not only see what was going on in all of them, but must know the details and the causes. He must know for himself. "Who relies on authority for argument," he writes, "uses his memory, not his reason." The dissection of the blood vessels of the scalp stimulated him to inquiry as to the causes of respiration, of the movement of the heart, of vomiting, of how food descends to the stomach and how it is evacuated; how man swallows, why he coughs, yawns and sneezes, why the legs go to sleep, and what makes the sensation of tickling. Any one of these problems could keep a physiologist busy for a life time. But for Leonardo such questions were only a few of those pressing forward for answer.

Flaubert said that Michael Angelo trembled when he came near marble. Leonardo must have trembled in every waking moment, for no circumstance was too trivial to stir the electric excitability of his mind. His execution could no more keep pace with his idea than sound can with light. He responded too freely to stimuli to permit of many finished products. But the high order of his mind is plain from the fact that in spite of his many occupations, everything he did showed the hand of the master craftsman, and every subject was enlightened by his thinking about it. Although he has gained little glory from it, he was easily the first man to acquire an accurate knowledge of descriptive anatomy. In the history of a science the place assigned to those who study it is determined by their influence on the development of the science rather than on what they know themselves. It is doubtful if Leonardo's work was familiar to many of his contemporaries, and there is no evidence that his drawings ever were of use to anatomists of his day or later. A recent contention that Vesalius secured Leonardo's drawings and changed them for his own use is too absurd to receive notice. The merit which is certainly his and the respect in which he is entitled to precedence over Vesalius, is that he used his great talents to break down the barriers which impeded medical progress, and that he inaugurated modern methods of anatomical investigation. A mention may be found in the note-books of a speech to be made to students, probably de la Torre's, in which he urges them to greater zeal in learning from dissection, which even the students were superstitiously afraid of, rather than to rely on authority. He made long-range guns and catapults, and devices for destroying strongholds and for defending them. With the self-confidence which is a part of genius, he submitted to his patrons the most pretentious plans for all military operations. Yet he hated war, calling it a bestial frenzy. And I fancy that he was taking a fling at martial practice when, in his defense of dissection, he compared the morals of the anatomist who reveres human beauty, to the morals of those who aim to destroy it. Throughout he shows the spirit of independence and inquiry, which always means originality of thought, and in those days meant personal courage as well. "Study science first," he notes, "for without it practice is nothing." He urges solitude, to permit the independent working of the mind. He practiced it as far as such a man can. He had no country, no family, and no woman's name was ever associated with his.

All his anatomical work reveals the painstaking thorough-

ness without which as a foundation no science can live. His inquiring mind was not satisfied with description; it must also compare. The bodies of men as opposed to women, the comparative study of different parts (e. g., the foot) in man and animals and birds, the differences of structure at different ages, the protective intentions of nature, as shown by the nerves running along the sides of the fingers, instead of on the front or back, all were studied or noted for study by him. He observed the differences in the blood vessels in youth and in age, and so foreshadowed the recognition of that disease which kills more people over fifty years of age than any other.

Had his accomplishments been less burdensome, had his genius been less universal, had he been permitted to make generally accessible to others what he knew himself, he might easily have shown himself to be as great an anatomist as Vesalius and still have had time to paint the Mona Lisa. Then the honor of founding modern anatomy would have belonged to Italy rather than to Belgium.

EMBRYOLOGY AND OBSTETRICS IN ANCIENT HEBREW LITERATURE.*

By DAVID I. MACHT, M. D.

The origin of life, the development of the human being, the birth of the babe and the growth of the child have always occupied a prominent place in the literature and religions of all primitive peoples, and in none a more important one than in Judaism, which considers the injunction "be fruitful and multiply" (Gen. I, 28) as the first commandment of the Revelation, and the perpetuation of the race as the sacred duty of mankind, and which brands as crime and moral murder any interference with the normal development and growth of the species from its very incipient stage to the time of its birth. It is therefore not surprising to find that embryology and obstetrics receive more attention in the early Hebrew writings, and more particularly in the Talmud and the Madrashim, than any other medical subject.

References to the earliest stages of embryonic development are found as far back as the Bible. In Psalm CXXXIX, 15-16, we read:

> My being was not concealed from thee, when I was made in secret, when I was embroidered in the lowest parts of the earth. My undeveloped substance did thy eyes see; and in thy book were all of them written down—the days which have been formed, while yet not one of them was here.

And in Job X, 10-12, we find the following:

> Behold, like milk didst thou pour me out, and like cheese didst thou curdle me. With skin and flesh didst thou clothe me, and with bone and sinews didst thou cover me. Life and kindness didst thou grant me, and thy providence watched over my spirit.

The general Hebrew name for the product of conception is "peri habbeten" or "fruit of the body." The earliest stage in the development of the embryo is termed "golem," a name borrowed from the passage in the Psalm CXXXIX just quoted, and which literally translated means something "formless and rolled up"—an undeveloped substance. In the further development of the embryo various stages are distinguished by the Hebrew sages and are designated by special names. The first stage begins with the "golem" or undeveloped substance and extends through a period of forty-two days or six weeks. The fœtus at the end of this period is known as "shefir merukkam," or embroidered membrane, clearly referring to the developing ovum with its membranes. The physician Samuel, in the second century (?) studied the embryo at this stage; and we are told that the eyes, nose and mouth can now be distinguished, the whole creature resembling a "grasshopper." In the Tractate Niddah 25 a, we read:

> The wise men learned, what is a "shefir merukkam"? Its eyes are like unto the two dots of a fly and are separate from each other; its two nostrils are like unto the two points of a fly but merge into each other; its mouth is fine like unto a fine hair: and its hands and feet are still unfashioned.

A second stage is distinguished from the sixth week to the fourth month. The embryo is now called an "ubbar," a passive participle, meaning literally "something borne or carried." It is the ordinary Hebrew word for a "fœtus." So is the mother spoken of as "meubbereth," or one "loaded down"—gravid, and the period of gestation is known as "yemay-ha-ibbur," or the days "of being loaded down"—of gravidity. At this stage, we are told, one can recognize the fingers and toes, the hair and the nails, and also the genitalia (Niddah 25 a). The growth of the hair is an important step in the development. We read "the work is not permanent, until the hair hath cropped out" (Niddah 25 b).

With the fourth month, we come to the third stage in the development. The fœtus is now no longer "like unto a grasshopper," but looks like a human being, and is now spoken of as "welad," a child. This "welad" or child, on reaching the seventh month, is known as "welad shel kaymo," a "viable welad," or a child that can survive. The Hebrew scholars looked upon a seventh-month baby as capable of surviving. In the eighth month, the Aristotelian notion prevailed, that the chances were not so good as in the seventh.

A fully developed fœtus is known as "ben she-kallu chaddoshow," "a child whose months have been completed."

An abortion or miscarriage is known in Hebrew as a "nefel," or something dropped.

In regard to the maturation of the ovum, the ancient Hebrews seem certainly to have recognized that for the develop-

* Read before the Johns Hopkins Hospital Historical Society December 12, 1910.

ment of the primitive germ there must be a union of male and female elements.

"Three partners," we are told, "contribute to the development of man: the father and mother, and the Holy One, blessed be His name. The father soweth the white and the mother soweth the red; God giveth spirit and life" (Niddah 31). Of the male and female elements, it is the nuclei or "kernels," as the scholars put it, that are the essential parts. (Sabin III—Midrash Rabba. 3 M. 14.)

In regard to the order of development of various parts, the general opinion was that the head first developed, then the body, and other parts; but a few maintained that the center of development is the umbilicus, evidently bearing in mind the attachment of the cord with its nutrient vessels.

The position of the fœtus is briefly thus described: "In the first three months, the child is below (that is inside the pelvis); in the second three months it is in the middle (that is between the pubis and umbilicus); and in the last three months it is at the top or at the level of the umbilicus" (Niddah 30). This served well as a rough means of determining the age of the fœtus. The position of the child inside the membranes was regarded as perfectly free, that being the function of the amniotic liquid.

"It floateth like a nut-shell on the waters, and moveth hither and thither at every touch" (Mid. R. 3 M. 14).

The child at full term is graphically described as follows, in a passage which has become classical and is often quoted by Hebrew writers:

> Rabbi Simlai lectured: the babe in its mother's womb is like unto a rolled up scroll, with folded arms it lieth closely pressed together, its elbows resting on its hips, its heels against its buttocks, its head between its knees. Its mouth is closed; its navel open. It eats its mother's food, and sips its mother's drink; but it doth not excrete for fear of hurting. Now when the time hath come, that which is closed is op'ed, and what was open closeth, behold the child is born. (Niddah 30 b.)

When we now turn to obstetrics proper, we are struck by the wealth of anatomical terms. The following is a list of the terms applied to various parts of the organs of generation:

Uterus = rechem.
Mons = kaf tappuach.
Vulva = erwah.
Rima pudendi = beth ha-sesarim (Niddah 66 b).
Vestibulum vaginæ = beth hizon (Niddah 41 b).
Orificium urethræ = lul (Niddah 17 b).
Hymen = be-thulim.
Ostium vaginæ = beth shinnayim.
Vagina = beth teref, beth rechem (Niddah 64 a).
Septum vesico-vaginale = karka prozdor.
Canalis cervicis uteri = mokor (Niddah 41 a).
Cavum uteri = cheder, beth herayon.
Fœtal membranes = shefir.
Placenta = shilyoh.
Ovary and tube = shelil shel bezim (Bezah 7 a).

The diagnosis of pregnancy was made practically by the same signs as now. The signs of pregnancy are divided into two classes: the positive signs and the presumptive signs. The positive signs were regarded as coming from the fœtus itself, the perception of its movements, the palpation of its parts. The chief presumptive signs were the suppression of menstruation, the appearance of colostrum, changes in the size and consistency of the uterus, and various subjective symptoms. A peculiar gait is spoken of, as characteristic of a possible pregnancy. Some obscure passages in the treatise *Niddah* seem to refer to what may be taken as a molar pregnancy or "hydatidiform mole," and there are certainly references to what may be regarded as extra uterine pregnancies.

The signs of former pregnancies, or of labor recently gone through, are cervical and other tears, and the presence of rests of placenta or membranes.

An intact hymen, though a presumptive evidence of virginity, is not regarded as an absolute proof. Cases are described of coitus with unruptured hymen (Chagiga 15 a).

Menstruation plays such an important rôle in the ritual life of the Jews, that a separate paper could be written on the subject. Here we shall merely mention a few salient points.

The age of puberty is by Jewish law set for the male at the completion of his thirteenth year, for the female at the end of her twelfth year. In the Orient, as is well known, menstruation begins at an earlier age than in the Occident. As signs of puberty were regarded the growth of pubic and axillary hair, development of the breasts, elasticity of the mamilla, pigmentation of the areola and various changes about the genitalia.

The type of menstruation was studied especially in regard to a determination of the time of its approach. The Jew is required by law to separate himself from his wife a day before the approach of her menses, and not to approach her until after she has dipped in the ritual bath or "mikewah" seven days after their cessation. Three types of menstruation were distinguished: In the first type, the periods return at certain definite regular intervals of time; in the second type, the return is not so regular as to time, but is preceded by various premonitory symptoms or signs, such as headache, pains in the abdomen, backache, heaviness in the limbs, premenstrual chills and fever, etc.; in the third type are put all the irregular cases.

Infantilism and under-development, with their consequent amenorrhœa and sterility are treated under a special heading called *Ai-lo-nith*. In connection with amenorrhœa and dysmenorrhœa I may mention their treatment by the employment of a reed or a stem, much like the stem-pessary employed by modern gynecologists not so many years ago.

The duration of normal gestation was given by the Talmudists as 271 days, or 9 months of 30 days each. There may, however, be variations, and a pregnancy of 12 months' duration is cited (Niddah 27 a and Jebamoth 80 b). As a mnemonic the length of pregnancy is expressed by the Hebrew word for pregnancy—H E R A Y O N. In Hebrew, as in Latin, numbers are expressed by the letters of the alphabet and the numerical value of the Hebrew word for pregnancy is 5 + 200 + 10 + 6 + 50 or 271 days.

The course of normal labor seems to have been an easier one among the ancient Hebrews than nowadays. "Ere the midwife cometh in unto them they are delivered" (Exodus I, 19). Severe labor pains were regarded as signs of divine wrath and punishment, and the prophets often employ this figure of speech in their utterances.

Four cases of dystocia or difficult labor are mentioned in the Bible. The first is that of Rebecca giving birth to her twins (Genesis XXV, 24). The second is that of Thamar (Genesis XXXVIII, 27), also giving birth to twins. The third is the birth of Benjamin (Genesis XXXV, 17) in which his mother Rachel succumbed. The fourth is the case of the wife of Phineas (I Samuel, IV, 19) of which we read:

And his daughter-in-law, the wife of Phineas was with child, near to be delivered; and when she heard the tidings concerning that the ark of God had been taken, and that her father-in-law and her husband were dead, she sank down and gave birth; for her pains came suddenly upon her.

Women in labor were attended by midwives, called "meyaldoth" or birth helpers, "chachomoth" or wise woman, and "chayoth" or life bringers. Physicians assisting in confinement are not mentioned in the Bible but are referred to in the Talmud.

The birth took place on a special kind of couch or stool—the "mashber." The midwife delivered the child and cut the cord, bathed the infant (Ezekiel XVI, 4), rubbed it with salt and wrapped it in swaddling clothes (Job XXXVIII, 91).

In case of asphyxiation the Talmudists recommend stroking the cord gently towards the infant before cutting it, and in extreme cases trying resuscitation by direct inflation of the infant's lungs (Sabbath, 130 and 150).

Multiple pregnancies are frequently mentioned. Twins were common, and in Egypt we are told the Hebrew women gave birth to sextuplets (Midrash Shemoth, and Rashi Exodus I, 7).

Superfecundation and superfœtation are both mentioned in the Talmud and are of medico-legal importance. The Talmudists held that a superfecundation occurring within forty days after the first conception may lead to normal twins; whereas after forty days one of the twins will thrive at the expense of the other. After the third month superfecundation cannot take place. We read (Berachoth, 60): "From the 40th day until after the 3rd month, one shall pray that there arise no 'sandol' (fœtus papyraceous or compressus); that she may not conceive a second child and so interfere with the development of the first."

With reference to superfœtation the law prohibits the marriage of a widow or a divorced woman who is pregnant until after the birth of the child (Jebamoth, 36 b-42 a; Sota, 26 a).

A word or two as to malformations and monstrosities. Quite a number of malformations and monstrosities are mentioned in the Talmud. We read of a fœtus with a human face and animal body, of a monster with a single eye, of an acephalos, of various malformations of the head, of partial extrusion of viscera, etc. Of special importance are various forms of hemaphrodites. These give rise to legal complications in cases where certain duties are limited to one sex only. A separate chapter in the Mishna under the title Androgynes is devoted to this subject.

Finally, a word in regard to obstetrical operations. Three kinds of operations are mentioned in the Talmud. The first was a destructive one—embryotomy, which consisted in the cutting up of the dead fœtus and extracting it piecemeal. The other two aimed at the saving of both mother and child. One was called "kariyath habbeten" or the cutting open of the abdomen, and was nothing more or less than the classical Caesarian section. The other operation called "yozay dofan" or delivery through the side, also aimed at the saving of both mother and child, but its exact character is a matter of dispute among Hebrew archæologists.

Before concluding, a word as to the Hebrew ideas on heredity and the recently much agitated so-called new but really old subject of eugenics. Freedom of will is, of course, the foundation of the Jewish as well as of all religions. "All is in the hands of God, except the fear of God," is a famous Hebrew saying. Man makes himself! And yet, the Hebrew sages recognize too well the importance of heredity. The sins of the parents are but too often visited on their children and their children's children unto the third and fourth generation, and that both morally and physically, hence a well-known Talmudic saying (Baba Mezia, 75 a): "Seest thou a wise man, whose son is wise, and whose son's sons have been brought up in the ways of wisdom—from their house wisdom shall not depart."

And that is indeed the natural explanation of the numerous Hebrew laws and customs pertaining to marriage and marital relations. The Jewish law does not shrink from the problems of social hygiene, but takes them up and analyzes and discusses them with exactly the same minuteness and exactness as the laws pertaining to the observance of the Sabbath and holidays, the dietary laws, the agrarian laws, the laws pertaining to the giving of charity. The body is not the sordid instrument of sin to be curbed and subjected, stunted and worn out by penitence and castigation; nay, it is the sacred abode of the spirit, and all its normal physiological functions are regarded as wholesome and intended for good. So is the procreative faculty, when subserving its true purpose—the rearing of a sturdy race of servitors to God. With such an end in view it is a sacred duty.

The Torah or the law thus frees us from the fetters of materialism, yet guards against the barrenness of an ascetic life, and consecrating all our activities to an exalted, noble end, uplifts mankind above mere dust. The ordinances concerning menstruation, the rigid laws enjoining periodic separation and purification in married life have all this end in view—to use the means, only as means, not for themselves, but for the furtherance of higher, nobler ends. No wonder, then, one ancient Hebrew sage styles them as ordinances of such momentous, far-reaching importance, compared with which astronomy and geometry are only "after-courses" in the School of Wisdom.

What the results of such a conduct are is not for me here to proclaim.

That, history has shown; that, history still shows: and that, so long as Jew is loyal to his heritage, history will continue to demonstrate.

Kislev, 5671.
December, 1910.

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ON DISSEMINATED CASEATING TUBERCULOSIS OF THE LIVER.

By William Sydney Thayer, M. D.,
Associate Physician, The Johns Hopkins Hospital, Baltimore.

Focal tuberculosis of the liver is a condition rarely giving rise to recognizable clinical phenomena. Those instances which are detected during life are, for the most part, large, solitary, conglomerate tubercles or tubercular abscesses. Disseminated caseating tuberculosis, while not uncommon, especially in children with intestinal and mesenteric lesions, is not often recognized *intra vitam*.

Rolleston[1] says: "There are very seldom any definite symptoms pointing to the liver."

Brown[2] says: "Complications of the liver have more pathological than clinical importance."

Hale-White[3] describes the condition purely from an anatomical standpoint and says: "This form of tubercular disease does not give rise to any clinical symptoms, as there is no damage to a sufficient number of ducts to cause jaundice."

Ebstein[4] says: "But also in these very rare cases (large conglomerate tubercles), tuberculosis of the liver has a purely anatomical interest."

The recent observation by the writer of an instance of tuberculosis of the liver where, during life, the hepatic changes stood in the foreground of the clinical picture would seem to justify a brief note.

M. B. (Med. No. 22216), a colored woman of 49, was admitted to the hospital on February 11, 1908, complaining of pain in the right lumbar region and in the back. Her family history was unimportant, excepting that her husband had died of tuberculosis 26 years ago. She had had measles in childhood; had been married 28 years: had had two children, one of whom died of tuberculosis. In July, 1902, a hystero-myomectomy was performed for sub-mucous myoma of the uterus, tubo-ovarian abscess and follicular salpingitis.

About five years ago, she had begun to suffer from rather ill-described pain in the left side which had continued. She had had a slight cough with occasional blood-streaked expectoration and increasing dyspnœa on exertion; night sweats for two years, constipation. About two months ago, *there was slight jaundice of the conjunctiva, lasting about a week.*

On physical examination the thorax was clear, except for a few scattered sibilant râles. The abdomen was full and on deep bimanual palpation there was an indefinite sense of fluctuation in the right flank, although the percussion note was tympanitic, even in the flanks. The border of the liver was not palpable.

Blood count:

R. B. C.	4,136,000
W. B. C.	6,120
Hb.	49%

Differential count:

Small mononuclears	7%
Large mononuclears	3
Transitionals	0.5
Polymorphonuclear neutrophiles	87
Polymorphonuclear eosinophiles	0.5
Unclassified	1

Stool: semi-fluid, light yellowish-brown. On standing, the upper third was fluid, the lower two-thirds, a brown and granular material. No parasites or eggs in the sediment; few cholesterin crystals.

The urine was increased in quantity and contained a trace of albumin and a good deal of pus and, considering the resistance in the right flank, it was thought well to catheterize the ureters. The patient, however, refused. An X-ray plate of the right side was taken which was broken in developing. By this time, the suspicion that the resistance in the right side might depend upon a renal mass having passed away, no further X-ray examination was made.

The temperature during the patient's stay in the hospital was irregular, ranging from normal or a point slightly sub-normal, often to 103° F., sometimes to a point above this. It was generally of an hectic character.

The urine continued increased in quantity, the specific gravity ranging from 1.002 to 1.010. Albumin was sometimes absent but often present in a slight trace, and occasional hyaline and granular casts were found in the sediment.

The blood pressure ranged from 120 to 158 mm. Hg. while the patient was in bed and resting.

March 22. Blood count:

R. B. C.	3,636,000
W. B. C.	6,420
Hb.	70%

March 29. Blood count:

R. B. C.	3,776,000
W. B. C.	6,840
Hb.	63%

On April 1, the author noted that the abdomen was held so rigidly that palpation was difficult. There was, however, a dis-

[1] Diseases of the Liver, etc., Phila., N. Y., London, 8°, 1905, 342.
[2] Osler's Modern Medicine, Vol. III, p. 320.
[3] Allbutt's and Rolleston's System of Medicine, Vol. IV, Pt. I, p. 199.
[4] Ebstein-Schwalbe, Handbuch der praktischen Medizin, 2 Aufl., Stuttg., 1905, Bd. II, 434.

tinct resistance at the right costal margin and the sense of an indefinite mass.

The patient was discharged at her own request, on April 4, 1908, with a diagnosis of chronic nephritis and possibly tuberculous peritonitis. The fever still continued.

She returned to the hospital on August 10, 1908 (Med. No. 22989). On this occasion, she had complained for about a month of swelling of the legs, feet, and abdomen, of tenderness in the right upper abdominal quadrant, and of fever and night sweats. There had been a slight cough, but little expectoration; there was constipation. There was slight puffiness of the eyelids, and moderate œdema of the ankles and legs. Slight enlargement of posterior cervical, axillary, epitrochlear and inguinal glands. The lungs showed a few crackling râles at both bases. The abdomen was full, measuring 88 cm. in the umbilical line. It was tender on palpation and had rather a doughy feel; evident movable dulness.

On August 29, Dr. Futcher observed that the liver was distinctly felt 10 cm. below the costal margin in the mamillary line and 8.5 cm. below the xyphoid; 3 cm. above the umbilicus in the median line. There was no special abdominal tenderness and no masses were to be felt. There appeared to be slight impairment on percussion at the right apex with harsh breath sounds and a few medium moist râles at the end of inspiration. The temperature was irregularly continuous and remittent.

The urine was of rather low specific gravity and showed a trace of albumen and hyaline and granular casts. The diagnosis on this occasion was again "Chronic nephritis; tuberculous peritonitis (?); enteroptosis."

The patient returned again on March 12, 1909 (Med. No. 23828). According to her statement, she had remained in fairly good condition until about four or five weeks before admission when she began to complain of diarrhœa, weakness and loss of appetite. There had been a little blood and mucus in the stools and later, some loss of control over the sphincter. There had been no abdominal pain; no cough; no shortness of breath. Two months before she had been troubled for a time by sweating at night. On entrance the temperature was normal but soon rose, remaining irregular and remittent while she was in the hospital, ranging from 99° to 102° F. On physical examination, she was moderately well nourished, but had obviously lost considerable weight. There was slight dulness at both bases with numerous moist crackling râles. The heart was in no way remarkable. The abdomen dome shaped, much distended. The edge of the liver was seen to descend with inspiration, and the edge firm and irregular, was easily felt to the right of the median line. The surface of the liver felt rough though no large masses were to be felt. The flatness extended from the 5th rib to a point 11 cm. below the costal margin in the right mammillary line and 12 cm. below the tip of the xyphoid process. Dulness on the left side shifted with position.

Blood count:

R. B. C.	3,444,000
W. B. C.	4,600
Hb.	63%

The stools, repeatedly examined, were semi-solid and fluid, showing a certain amount of mucus, evidences of occult blood and occasionally a few red corpuscles. Microscopically, there was no excessive amount of fat; no amœbæ were found on careful examination.

The blood pressure was rather low—95 to 120 mm. Hg.

The leucocytes were normal in number, even sub-normal, 4500, on the day before death.

An Ewald test meal showed 100 cc. of thin watery fluid which separated into two layers, the upper consisting of a turbid, dirty yellow liquid and the lower of finely-divided food elements. It was acid; total acidity, 18; free hydrochloric acid, absent; lactic acid, absent; test for occult blood, negative. Microscopically, fat droplets were present in considerable numbers; starch granules, epithelial cells and vegetable fibres.

The Wassermann reaction was negative.

The urine apparently rather reduced in quantity, showed a specific gravity of 1.011, a heavy ring of albumen, and numerous hyaline, finely and coarsely granular casts.

On the 18th of March, the writer noted that both apices showed a slight tubular modification of the respiratory murmur, and fine crackling râles were detected, especially above the left clavicle,

DISSEMINATED CASEATING TUBERCULOSIS OF THE LIVER, WITH CAVITY FORMATION, IN AN ADULT.

as well as a peculiar superficial crackle, which sounded almost pleural in character over the whole left chest. There was little modification on percussion of the bases behind. Numerous fine râles were to be heard at the apices and occasional crackles throughout both backs. Abdomen, large and full. Flanks bulged. The umbilicus protruded. Diastasis of recti. Respiratory movements free. Edge of liver sharp, firm and smooth, but not quite so sharp in the right flank as elsewhere. Upper limit of liver flatness, 6th space in mammillary line. Lower border, 10 cm. below the costal margin in the mammillary line, 9 cm. below xyphoid; notch, well felt. No fluctuation detected.

March 21. The patient had been growing progressively weaker and for three days, the posterior parts of both lungs had been filled with fine, moist râles although there had been no dulness. The heart has been markedly irregular at times. There appeared to be no fluid in the abdominal cavity.

The patient became gradually weaker, the anæmia, more marked.

Blood count:

R. B. C.	3,000,000
Hb.	50%

Numerous fine râles appeared throughout the chest. At 8.30 p. m., she died.

In *summary*, then, the history is that of a colored woman of 19, who, a little over a year before her death, came to the hospital suffering from remittent and intermittent fever and vague abdominal manifestations—tenderness, resistance. Six months later, she returned with a history of diarrhœa of four or five weeks' duration: weakness and general debility. There was irregular fever with morning remissions or intermissions. The liver, which was somewhat prolapsed, was much enlarged and firm and there was a well-marked anæmia of a secondary type. There was, at times, occult blood in the stools which showed considerable mucus. No excess of fat or fatty acids.

The diagnosis of tuberculous peritonitis, made on her previous entry, seemed reasonable when one considered the race of the patient, the fever, and the general abdominal symptoms, the diarrhœa suggesting a tuberculous enteritis, but the hepatic enlargement seemed difficult to account for on the basis of tuberculosis, although the possibility of a fatty cirrhotic liver was considered.

Considering the age of the patient, the degree of anæmia, the progressive enlargement of the liver, its firmness and slight irregularity, one could not but think of the possibility of a neoplasm of uncertain origin. The well known occurrence of fever in association with hepatic neoplasms would not have been against this diagnosis, although no suggestion as to the primary seat of such a growth could be found beyond the possible significance of blood and mucus in the stools.

Another possibility which suggested itself was that the case might be one of amœbic abscess of the liver. The slight fever, the diarrhœa, the jaundice present at one time, although amœbæ had not been found in the stools, and the progressive hepatic enlargement formed a clinical picture not unlike that which is occasionally seen in such cases.

The necropsy was performed on March 22 by Dr. Winternitz (No. 3188).

(Abstract.) Anatomical diagnosis: *Tuberculosis of the mesenteric and retroperitoneal lymph glands with involvement of the receptaculum chyli; chronic adhesive peritonitis; chyliform ascites; tuberculosis of the spine with abscess formation; generalized tuberculosis; extensive tuberculosis of the liver with cavity formation; tuberculosis of the spleen and liver; tuberculous broncho-pneumonia, caseous and gelatinous; fatty degeneration of the liver; chronic fibrous pleurisy; chronic diffuse nephritis; arterio-sclerosis; chronic fibrous myocarditis; thrombosis of ovarian vein.*

The peritoneal cavity contained a considerable amount of chyliform fluid which was extremely milky in appearance. The omentum was definitely plastered to the parietal peritoneum but was not evenly adherent, so that encapsulated areas appeared in which the above-described fluid was found. The intestinal peritoneum was not adherent either to the omentum or to the parietal peritoneum of the anterior surface, so that when the omentum was severed from its attachment, the abdominal contents were easily exposed and the intestines were found to lie almost entirely in the lower half of the abdominal cavity. A large mass was found in the upper portion of the abdominal cavity filling the entire epigastrium and the upper half of the umbilical region as well as the hypogastric region on the right side. This mass which proved to be the liver, was covered over its entire surface by adhesions which were formed by fibrous œdematous union between the peritoneal surface of the organ and the parietal peritoneum. The liver was closely bound to the diaphragm above on both right and left sides. The stomach was bound down by dense adhesions. The mesenteric lymph glands were extremely large and yellowish-grey. On section, they were rather firm and mottled, the greater part of their structure being composed of a rather friable yellowish substance which had a faint green tinge, while throughout one could see other areas which were slightly more translucent and depressed.

There was nothing remarkable in the heart.

The lungs showed a disseminated tuberculosis with larger areas of broncho-pneumonia here and there.

The spleen measured 10 x 6½ x 4½ cm. The capsule was everywhere adherent to the diaphragm and surrounding viscera. On section, the Malpighian corpuscles were indistinct, and smaller opaque yellow tubercles were to be made out.

The stomach, duodenum and pancreas showed nothing of importance.

The liver was considerably enlarged, measuring 30 x 28 x 10 cm. It was flabby, and the surface was covered with nodules varying from 0.5 to 1 cm. in diameter, which were yellowish-grey. On section, the liver was everywhere studded with these nodules, some of which were firm and yellow and caseous; many were, however, cavities showing greenish bile deposits in their centres. Many of these caseous masses were surrounded by thin, translucent, reddish-gray capsules. The remainder of the liver was pale. Lobulation was indistinct. The tissue about the hepatic vein was reddened and the peri-portal veins were everywhere very visible. Small tubercles were also scattered throughout the liver tissue, many surrounded by transparent gelatinous zones.

Kidneys: The right measured 11 x 6½ x 3½ cm. The capsule stripped off with slight difficulty, leaving a rather smooth, pale surface. On section, the kidney was everywhere studded with yellow nodules which, in some spots, were as large as 1 cm. in diameter. Most of these were small, measuring 2 mm. The cortex of the kidney was swollen, averaging 7 mm. The striations for the most part were regular and the parenchyma was extremely pale, showing here and there yellow irregular areas more opaque than the surrounding. The glomeruli were prominent and transparent, pale pink in appearance. The left kidney resembled the right in every respect.

The thoracic duct, which was dissected out carefully was found to be in communication with a mass of glands which lay in the region of the receptaculum chyli.

Nothing remarkable in the bladder.

The glands lying over the spine on the right side from the eighth dorsal to the first and second lumbar, were soft and a puriform fluid escaped from them. There was tuberculous caries of all the vertebræ from the sixth thoracic to the first lumbar. There was no essential curvature of the spine.

Examination of the ascitic fluid showed that, after standing for several hours, it had become more milky in appearance. Specific gravity 1.018. Microscopically, there were large numbers of degenerated peritoneal epithelial cells. In addition, a few small round cells and some fat globules were seen. No tubercle bacilli were found.

The liver, microscopically, showed many large areas of caseation, some involving bile ducts the remains of which could be seen in the necrotic ulcerated centre. The remaining liver tissue showed an extensive fatty degeneration. Around some of the larger tubercles, there was a zone of tuberculous granulation tissue which was rather fibrous showing here and there well-formed tubercles. This doubtless represented the translucent grayish zone which was observed about the large tubercles in gross. There was no definite cirrhosis throughout the remaining portion of the liver, but one found here and there small patches of cellular tissue which were possibly healing tubercles. In these one found no areas of degeneration but a mass of rather well-preserved spindle cells and round cells. Among these numerous blood vessels might be seen. Some of these were evidently the tips of well-formed tubercles. Others of the larger tubercles showed a dense mass of fibrous tissue surrounding a caseous centre. The fibrous tissue, however, was not well preserved and had apparently undergone hyaline degeneration. Tubercles, however, in these areas, were definitely circumscribed and were apparently old processes that are walled off. In other areas, masses of miliary and conglomerate tubercles were to be seen which seemed to proliferate irrespectively of any general position. These did not involve the bile ducts and were not in close relation to any particular portion of the vascular system.

The kidneys showed here and there dense bands of fibrous tissue extending in from the capsule. Here the renal tissue had undergone definite atrophy, the tubules being very much smaller than in the surrounding tissue. Glomeruli might be found in this mass as dense hyaline staining masses. In fact, the glomeruli seemed to show most marked changes. One found in many places, where the uriniferous tubules were apparently not markedly degenerated, that the glomeruli were large, filling up, as a rule, the entire capsule. In some places, there was a slight exudate between the glomerular capsule and the tuft, but this was not often found. There were not very many intermediate stages between glomeruli which appeared normal and those in which there was a dense fibrosis. Where these were to be seen, the thickening seemed to start in the glomerular capsule which proliferated at the expense of the glomerular tuft. The uriniferous tubules throughout stained diffusely red. Their lumina were dilated and contained serous-like material and many casts. Many of the epithelial cells of the tubules showed large vacuoles which filled the entire cells, and smaller vacuoles might be seen near the basement membrane, but not as large as those which have been described. In some places the entire tubules showed this vacuolar degeneration.

To summarize then, we have before us the history of a colored woman, 49 years of age, with a record of rather indefinite abdominal pain of a year's duration and almost continuous remittent or intermittent fever of a moderate degree, with sweating at night and progressive emaciation. Examination of the thorax showed little beyond the appearance toward the end, of rather diffuse fine râles throughout the lungs. During the last eight months of the patient's life there was a steady enlargement of the liver which finally extended to a point 10 cm. below the costal margin in the right mammillary line. It was somewhat tender and very firm, and, on one occasion, slight irregularities of surface were noted. The border which was distinct, seemed a little blunter in the right mammillary line. There was considerable anæmia of a secondary type, but without leucocytosis, a persistent albuminuria and cylindruria without polyuria but with a rather low specific gravity, and, in the end, diarrhœa with mucus and occult blood in the stools.

The progressively enlarging liver, the age of the patient, the anæmia, the fever which after all, is common in hepatic neoplasms, all led us to lean toward this as a possible diagnosis, despite the fact that beyond the diarrhœa with occult blood in the stools no suggestion as to the seat of a primary lesion was to be made out.

The indefinite abdominal pain, tenderness and fever, together with the diarrhœa occurring in a colored woman were strongly suggestive of peritoneal tuberculosis, despite the absence of definite pulmonary signs, but the progressively and apparently great enlargement of the liver did not appear to us to depend upon tuberculosis alone. It was thought that a rolled-up omentum might be adherent to the liver, thus increasing its apparent size, but the sharp border of the liver was against this.

A steadily enlarging liver, with persistent, slight fever, even in the absence of leucocytosis, is by no means unusual in amœbic abscess which occurred to us as a possibility.

Syphilis was ruled out by the absence of a Wassermann reaction and by the fact that anti-luetic treatment had been without result.

The case was, indeed, presented to the class with the main possibilities as to diagnosis set forth in the order named: hepatic neoplasm; amœbic abscess of the liver; peritoneal and intestinal tuberculosis with a rolled-up omentum adherent to the liver in such a manner as to exaggerate its apparent size.

The anatomical appearances, well illustrated in the plate, are rather remarkable in their extent. A disseminated caseating tuberculosis of this degree in the liver of an adult is most unusual. But the feature of the case which is of special importance is that such disseminated caseous tuberculosis of the liver should have given rise to a tumor sufficient to constitute the central figure in the clinical picture.

It is also important to note that for a week at least during the course of this case there was jaundice—a rare manifestation in hepatic tuberculosis.

In conclusion then, it may be emphasized that disseminated caseating tuberculosis of the liver in an adult may be associated clinically on the one hand with appreciable jaundice and on the other with hepatic enlargement sufficient to form the most striking feature of the clinical picture.

A PEPTID-SPLITTING FERMENT IN THE SALIVA.

By Louis M. Warfield, A. B., M. D.

(From the Laboratory of the Milwaukee County Hospital.)

While experimenting with the glycyltryptophan test described by Neubauer and Fischer, some very inconstant results were found which led to the trial of saliva in the hope that an explanation might be found.

The presence of a peptid-splitting enzyme in cancer tissue from the stomach had already been shown by Emerson. He demonstrated its presence by taking macerated cancer tissue, dividing it into two portions, one of which was heated to 80° C. In the unheated portion the digestion of albuminous substances was carried beyond the albumose stage.

In 1909 Neubauer and Fischer utilized this property of cancerous tissue to perfect a test which they thought was of value in the diagnosis of cancer of the stomach. They called attention to four sources of error:

1. Presence of tryptophan in the stomach contents.
2. Presence of peptid-splitting bacteria.
3. Presence of trypsin (pancreatic juice).
4. Presence of blood.

They also affirmed that an HCl content of over 0.36 per cent vitiated the test. They concluded that "1. In the contents of a carcinomatous stomach there is present a ferment which with pepsin splits glycyltryptophan. 2. This ferment is destroyed by an acidity of 0.36 per cent HCl. 3. The presence of this ferment can be used for purposes of diagnosis."

The test is said to depend upon the presence in the carcinomatous tissue in the stomach of a peptid-splitting enzyme which carries protein digestion of peptids to the amino-acid stage. Neubauer and Fischer used the di-peptid glycyltryptophan, a combination of glycocoll and tryptophan. The tryptophan when split off can be readily recognized by a specific color reaction with bromine vapor or bromine water.

Normally pepsin digestion in the stomach is not carried beyond the stage of albumoses and peptones. When the chyme is acted on by the trypsin of the pancreatic secretion, there is further hydrolysis of the peptones into the amino-acids. In the complete digestion of coagulable proteins the stages are: proteins, meta-proteins (commonly called albumoses), proteoses (albumoses), peptones, polypeptids, amino-acids. We are concerned only with the polypeptids. These substances were discovered by Emil Fischer. He succeeded in linking together the amino-acids, the generic formula of which is R—CH—NH_2—COOH, with one another. This combination takes place between the carboxyl group of one amino-acid and the amido group of the other with the loss of one molecule of water. The most complex polypeptid yet produced is one containing 15 glycocoll and 3 leucine residues. The name polypeptid is applied to all the group of combined amino-acids. These large molecule peptids are much like the albumoses and peptones in that they do not crystallize, are precipitated by ammonium and zinc sulphate, and give the biuret test.

Tryptophan is indol-*a*-amino-propionic acid, which in combination with glycocoll forms the di-peptid glycyltryptophan. When this is acted upon by a ferment which is able to split the peptid, it is decomposed into the two amino-acids.

H. Fischer showed that in the normal stomach pepsin splits albumin into peptid chains which react alkaline to litmus. These combine every one with one molecule of HCl, and then react acid to litmus. Normal peptic digestion ceases at this stage. He also found that in stomachs in which there was cancer this chain is broken probably by a ferment. The free HCl vanishes but the total acidity may rise. This is due to the power of the amino-acids to bind the free HCl.

Lyle and Kober studied 21 cases with the glycyltryptophan test.* They conclude that "Results with the test have been satisfactory. A repeated negative reaction is very valuable. When the test is positive the complication of a regurgitation of trypsin must be thoroughly investigated. No deductions ought to be drawn from less than three tests."

Weinstein worked with the test and suggested some modifications. He disagrees with Neubauer and Fischer that when tryptophan is in the fresh contents the specimen should be rejected. He believes that the presence of tryptophan in the recent contents shows the presence of the peptid-splitting enzyme and the glycyltryptophan test is then superfluous. With this I agree. He also thinks that the danger from peptid-splitting bacteria is exaggerated as well as the danger from occult blood. It is difficult to test for bile in the gastric contents. He agrees that a specimen containing macroscopic bile should be discarded. The danger is, of course, that there may be duodenal contents containing trypsin. This is to be guarded against. He prefers bromine water to bromine vapor.

* The test is performed as follows: Ten cubic centimeters of the filtered gastric contents free from bile, removed from forty-five minutes to an hour after an Ewald test breakfast, are placed in a vial with 2 cc. of glycyltryptophan in solution over which is a layer of toluol. This is placed in the thermostat for several hours. Two to 3 cc. are then taken out with a pipette, transferred to a test-tube, acidified with a few drops of 3 per cent acetic acid, and fumes of bromine or a small drop of bromine water added. Care must be taken to pour only a small amount of bromine fumes or to add only a small drop of bromine water. The presence of tryptophan is shown by a rose or reddish violet color. The further addition of bromine vapor or water will, in excess, produce a yellow color. Unless the bromine is added carefully, a little at a time, one might miss a very slight pink reaction. It is also well to allow the tube to stand several minutes, as a very faint reaction often becomes more pronounced on standing.

I have procured the substance from Arthur H. Thomas Company, Philadelphia, Pa. It is expensive, six dollars for one dozen tests. One can now obtain it in bottles containing material enough for twenty-five or fifty tests.

I have also found this a better method. Weinstein prefers a meal of bread, butter, beef and sweetened tea which he removes after 3 to 4 hours and tests directly for tryptophan. If tryptophan is negative he places the filtered contents in the thermostat and tests again after 24 hours. From his work (150 tests) on 63 cases suffering from cancer of the stomach, and other diseases of the stomach, he concludes that the tryptophan test is a valuable sign in the diagnosis of cancer of the stomach. It is a sign in itself. The negative reaction is of more value than the positive. The results are inconstant, he admits. Whether or not it is an early sign of cancer he does not know.

Kuttner and Pulvemacher used silk peptone in their work. It is very much cheaper than glycyltryptophan, and comparative results showed that the tests paralleled each other accurately. The reaction with the silk peptone depends upon the splitting of the substance by the hypothetical cancer ferment into amino-acids, chiefly tyrosin. This is recognized microscopically. Their process is tedious and doubtless will never be used to any great extent in the clinical laboratory. It is academically of interest. They made 163 tests on 92 persons with and without stomach disease. Seven gave definite results, 19 gave variable findings. Vomitus was examined in five cases. Their results were so variable they conclude that the presence of the reaction has no meaning for the diagnosis of cancer of the stomach. For example, in 14 cases clinically cancer of the stomach, the contents reacted five times positively and nine times negatively. In 25 examinations of material removed from the fasting stomach 13 were positive and 12 negative. They call particular attention to the regurgitation of pancreas secretion and the confusion of this with the peptid-splitting enzyme. They think that the test may be of use in the demonstration of the functioning power of the pancreas, particularly after the ingestion of oil.

Personal Observations.

The first case in which I tried the test with stomach contents and glycyltryptophan reacted positively on two occasions. There was no free HCl in the stomach contents, no evidences of bile. The clinical diagnosis was acute endocarditis. At autopsy the stomach, œsophagus and intestines were absolutely free from tumor. It was thought that in both the tests the influence of pancreatic secretion could be excluded, so my saliva was placed with the glycyltryptophan in the hope that some light might be thrown on the positive tests in a normal stomach. It was a great surprise to find that the saliva split the glycyltryptophan; the test was absolutely positive. No such action of the saliva could be found in literature. Only two enzymes have been described in saliva, ptyalin and maltase. Next my assistant's (C. M. J.) saliva was tested. It reacted negatively. With three separate lots of the test material, procured at different times, my saliva reacted positively. The reaction to litmus is definitely alkaline. Moreover, it was found that by dividing a specimen of my saliva, which had been well centrifugalized, into two parts, after heating one part to 100° C. and not heating the other, the heated portion did not split the glycyltryptophan, while the unheated portion gave a positive reaction. A control with distilled water performed at the same time was negative. How was the negative test with C. M. J.'s saliva to be accounted for? It was found that her saliva was acid to litmus.

It was thought that saliva from one who smokes might account for the positive test. This was shown to be false by the fact that the saliva of my assistant (R. T. G.) who never uses tobacco, gave also a definite positive result. The salivas of the six internes were then tested. Three are smokers, three never use tobacco. All reacted positively and all salivas were alkaline to litmus. Next the salivas of six nurses were tested. These were alkaline and these reacted positively.

The stomach contents of a patient, J. C. (Hosp. No. 8971), who has carcinoma of the stomach, in which there was no free HCl, but total acidity of 52, reacted negatively both to tryptophan in the fresh contents and with the glycyltryptophan on December 31, 1910. Again, on January 13, there was no tryptophan found in the fresh contents. On January 27, with no free HCl and a total acidity of 46, there was a most marked reaction to tryptophan. This was again found on March 3. This patient's saliva did not split glycyltryptophan, but the saliva of another carcinoma case (Hosp. No. 9098), in whose contents there was no free HCl, did split the di-peptid. It was found that the saliva of J. C. was acid, while that of S. was alkaline.

Tests made with stomach contents from a variety of diseases, and from R. T. G.'s and mine after an Ewald test breakfast, showed that when free HCl was present in amount from 0.05 per cent on, the glycyltryptophan was not split. On the contrary, of eleven cases containing no free HCl in the stomach contents all reacted positively but two. Both the negative tests occurred with contents which contained considerable lactic acid. One case (Hosp. No. 8588) was at first thought to be cancer of the stomach, but later was found to be chronic nephritis and arteriosclerosis; the other was J. C., who had acid saliva and total acidity of 52.

One patient, J. S. (Hosp. No. 9140), in whose contents there was no free HCl, gave negative tryptophan and positive glycyltryptophan reactions. Autopsy revealed no stomach tumor of any kind.

Another patient, J. K. (Hosp. No. 8753), with clinical diagnosis of cancer of the stomach, had alkaline stomach contents in which was no tryptophan but which split glycyltryptophan, giving a very positive reaction.

A case furnished by a colleague was rather curious. J. P. B., aged 51, was suspected of having a cancer of the stomach. There was constant absence of free HCl and low total acidity. At the Johns Hopkins Hospital two positive glycyltryptophan tests were obtained, and on these, together with his suspicious symptoms, a laparotomy was advised. In Milwaukee about one month later two tests were negative, but the free HCl was still absent. At operation no evidence of cancer was found. A few enlarged glands which were removed showed only irritative hypertrophy. The saliva in this case has not been tested.

Discussion of Results.

All who have worked with the test have reported most inconstant and variable results. The test has been found positive in achylia gastrica. This accords with the view here held that it is the swallowed saliva which is responsible for the splitting of the glycyltryptophan. This explains most of the discordant results. An occasional acid saliva would explain an occasional negative test, when it would otherwise be expected to be positive. An examination of the results invariably shows that when the stomach contents are acid, 0.05 per cent plus, the test is negative; when there is no free HCl it may or may not be positive. A high total acidity, combined HCl, as is here shown, accounts for some of the negative results, and the presence of relatively large amounts of lactic acid accounts for some other negative results. Still other negative results in contents showing no free HCl and a low total acidity are accounted for by the acidity of the saliva.

That there is a peptid-splitting enzyme in cancer juice seems to have been shown (Emerson, Neubauer and Fischer). The very fact, however, that cancer of the stomach is so often accompanied by absence of free HCl in the stomach contents is just the condition most favorable for the action of the salivary peptid-splitting enzyme.

From what glands, parotid or sub-maxillary and sublingual, this enzyme is secreted is not at present determined. Whether the splitting is caused by bacteria in the saliva has not been shown yet. Weinstein denies the possibility of bacterial action, and Neubauer and Fischer did not show positively that bacteria could split polypeptids, except after prolonged action for days. At just what temperature the enzyme in the saliva is destroyed has not been accurately determined. Heated to 100° C. it is destroyed.

Care was always taken to centrifugalize the saliva, but it did not appear that this precaution was necessary. Further work is now in progress, but enough has been done to warrant the following conclusions:

1. There is a substance in the saliva, probably an enzyme, which has the power to split glycyltryptophan.
2. This property of the saliva is lost when the saliva is acid or when it is heated to 100° C.
3. Stomach contents containing no free HCl may split glycyltryptophan.
4. Stomach contents which have a high combined acidity or which contain a relatively large amount of lactic acid fail to split the di-peptid.
5. In view of these facts the glycyltryptophan test is of no value in the diagnosis of cancer of the stomach.

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THE RELATIONSHIP BETWEEN THE NORMAL AND PATHOLOGICAL THYROID GLAND OF FISH.

By J. F. Gudernatsch.

(From the Department of Anatomy, Cornell University Medical College, New York City.)

Recent investigations of the thyroid gland of Teleosts have revealed a great many facts that may be of value to the comparative pathologist. The thyroid gland of these fish attracts at present a good deal of attention in cancer research, since it is often liable to cancerous degeneration, especially in artificially reared trout and salmon.

The normal anatomy of the gland was briefly described in a paper read before the meeting of the American Association of Cancer Research, November 27, 1909. * It was especially emphasized that one of the most striking features of the thyroid in bony fish is the absence of a connective tissue capsule, such as exists in other vertebrates. Later this fact was again pointed out by Marine and Lenhart. It will readily be seen that the absence of a capsule makes it rather difficult to define the normal extension of the gland. It would perhaps be better not to use the term "thyroid gland" at all in this group of animals, since physiologically isopotent units (follicles) are not so arranged as to form a closed organ, but are distributed over a wide area (Fig. 2 and Plate 1). This distribution varies not only with the species, but also with the individual, and is dependent entirely on mechanical influences, mainly pressure from the sides of the surrounding tissues,

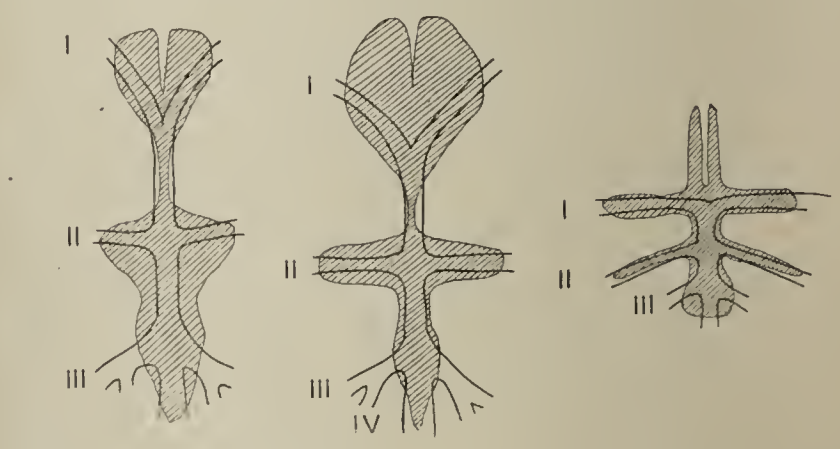

Fig. 1.—These diagrammatic drawings show the expansion of the thyroid gland in the three species: Oncorhynchus, Salvelinus and Opsanus. *I*, aortic bifurcation; *II*, *III* and *IV*, the second, third and fourth branchial arteries.

* An extensive analysis of the normal conditions of the Teleost thyroid will be found in Jour. of Morphology, V. 21, Suppl., 1911.

and pull enacted by the growing connective tissue fibers and blood and lymph vessels. The latter force works chiefly in the early development of the gland, when thyroid cells are carried off from the main point of growth to distant regions, where they form new centers of multiplication.

The thyroid gland develops around the stem of the ventral aorta (Fig. 1), in many species the main bulk lying between the branches to the first and second gill arches. This locality is filled with connective tissue and fat, and is enclosed dorsally by cartilages or bones and ventrally by muscles. Thus the region available for the thyroid tissue is rather limited, and therefore the follicles tend to fill every space that is offered by the surrounding structures. Not uncommonly follicles are found far from the center of thyroid development, invading muscles (Plate 1, *C*) or creeping into the crevices which exist between the osseous lamellæ of the bones in this region (Fig. 2 and Plate 1, *A*).

The thyroid gland of the Teleosts is thus a rather indefinite organ in its shape, having the tendency to lose its unity and break into numerous small parts. In some species, the trout and others, this tendency manifests itself most strikingly, so that thyroid follicles are found even far out in the gill arches along the gill filaments (Plate 1, *D*).

The spreading apart of the thyroid follicles over a wide area and the invasion of neighboring tissues are a normal feature and of no pathological significance. By such an invasion the surrounding structures are not destroyed. Often the term "invasion" is even incorrect. Thus Marine and Lenhart's statement that the normal follicles invade the bones is not appropriate, since they do not invade true bone or cartilage tissue, but merely the spaces that are present *between* the osseous or cartilaginous lamellæ (Fig. 2 and Plate 1, *A*). In their paper Fig. 6 demonstrates this fact definitely, although it is supposed to show a true invasion. On the other

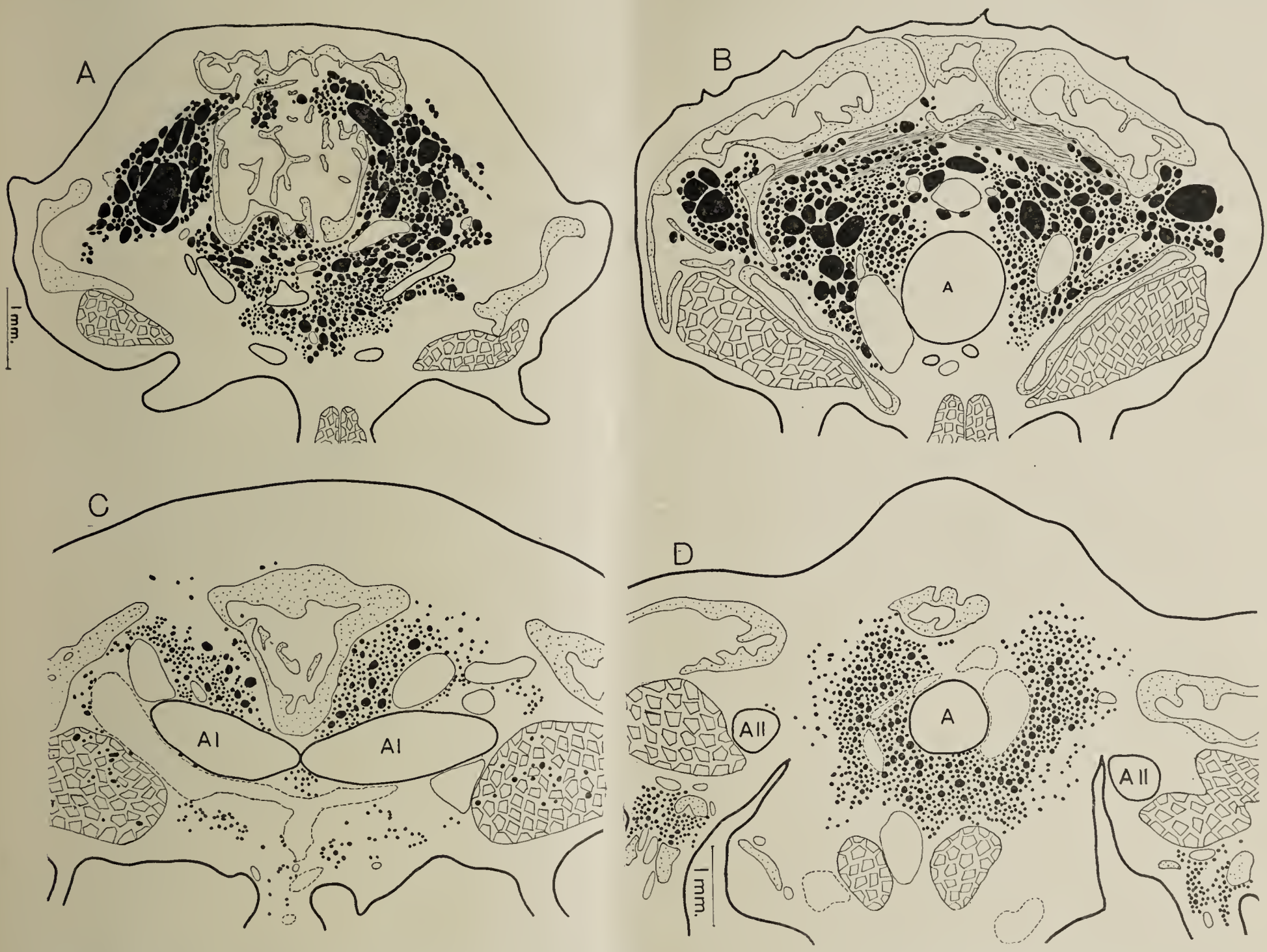

Plate I.—*A* and *B*, sections through the thyroid gland of Sarda. *A*, in the region of greatest extension anterior to the aortic bifurcation; *B*, near the second branchial arteries, the region of greatest extension. *C* and *D*, sections through the thyroid gland of Salvelinus. *C*, in the aortic bifurcation; *D*, near the second branchial arteries.

(Thyroid follicles in all figures shown in solid black. Transverse muscles lined. Longitudinal muscles in polygons. Skeletal parts stippled. Arteries in heavy lines. Veins in light lines. Lymph sinuses in broken lines. *A*, ventral aorta, *AI* and *AII*, branchial arteries.)

hand, Gaylord was able to show specimens in which thyroid tissue, belonging to a diseased gland, had actually invaded or infiltrated true cartilaginous tissue. The latter invasion, of course, is never seen in the anatomy of the normal gland, but is a strictly pathological feature. Whether or not it is due to a cancerous growth of the gland, may still be an open question. Strong evidence seems, however, to point in that direction.

Should the so-called thyroid carcinoma of brook trout be a cancerous growth and not a mere hyperplasia, as Marine and Lenhart believe, then the question of metastasis again demands the pathologist to keep in mind the lack of a capsule. Certainly no detached nodules in or around the gill region can safely be called secondary tumors, since such misplaced structures in all probability are merely parts of the primarily diseased gland. However, tumors on the tip of the jaw or around

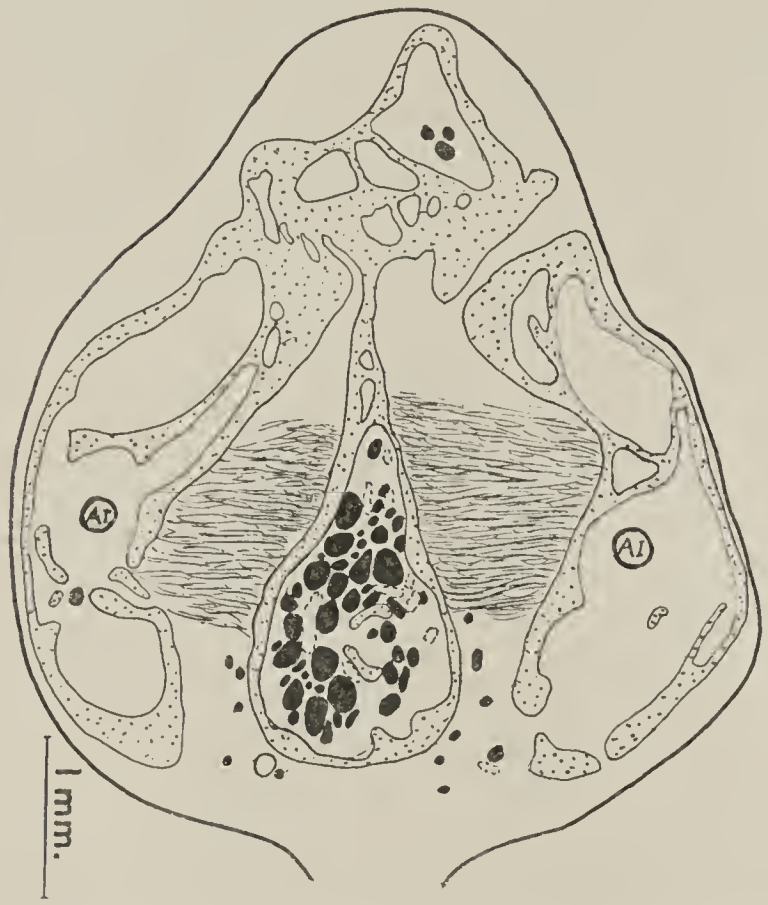

FIG. 2.—Section through the thyroid gland of Brevoortia, anterior to the aortic bifurcation. *AI*, first branchial arteries.

the anus, as Gaylord has found them, can hardly be explained as due to normally misplaced thyroid particles. Whether they are true secondary growths or simply implantations, further experimental investigations may show.

Histologically the thyroid gland of the Teleosts offers a great many interesting peculiarities. The size of the follicles varies between very wide limits. Aside from the fact that in young embryos it is naturally very small, the size of follicles cannot be taken as a reliable indication of the age of the fish. It seems much more probable that it is a sign of the age of the individual follicle.

The follicular epithelium varies from an almost flat to a very high, columnar type. It is different in each individual and may somewhat depend on the age and the physiological condition of the animal. Yet the type of the epithelium is not always uniform in all the follicles, sometimes very marked differences are found (Fig. 3). Even in the individual follicle the height of the epithelium may vary, probably due to different pressure from outside. It was now and then observed, that in oblong follicles the epithelium on the two longer sides would be lower than on the shorter ones.

The colloid material is sometimes present in all the follicles, in other glands it may appear in some only, in still others it may be entirely lacking. It, again, is no definite sign of the age of the animal, although it may be somewhat dependent on the age of the fish, its sex (egg-carrying females, for instance) and other inherent factors that need further investigation. The colloid certainly is a sign of the physiological state of the individual follicle, yet we do not understand it well enough to interpret our observations in a definite manner. There can be no doubt that all the follicles of a gland are not in the same state of physiological activity. Otherwise it cannot be explained why (Hürthle's) colloid-forming cells appear in some follicles only, sometimes in a

FIG. 3.—Section through the thyroid gland of Salvelinus fontinalis. Note the different heights of the follicular epithelium. Dia. 1:300.

group of neighboring follicles, so that we can easily distinguish "colloid zones" from non-colloid-forming parts of the gland.

In interpreting their results after iodin treatment of the thyroid gland of the pike Marine and Lenhart lay great stress on the histological appearance of the treated and not treated glands. Yet from the above discussion it seems obvious that the anatomy of the gland as well as its histology, as far as the type of epithelium and the colloid formation are concerned, makes it rather difficult for the microscopist to distinguish a normal from a hyperplastic, and the latter in turn from a "reverted" thyroid gland in these fish.

The presence or absence of the colloid material has no significance whatsoever. If all glands, the follicles of which spread out far from the main bulk even into the gill region, are highly hyperplastic, then, according to Marine and Len-

hart, the colloid material should be nearly or entirely absent in them. Yet it is present throughout the gland.

The type of the epithelium is also a perfectly unreliable guide in regarding a gland as hyperplastic. When, of course, the epithelium shows marked foldings and protuberances into the lumen, the hyperplastic condition is evident.

Further studies on the carcinoma of the fish thyroid will have to take into account the peculiar anatomy and histology of this organ in the Teleosts. Many conditions which might be regarded as pathological may prove to be normal as soon as our knowledge of all the factors involved is sufficiently broadened.

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TUBERCULAR BURSITIS.

TWO UNUSUAL CASES.

By SYDNEY M. CONE, A. B., M. D., Baltimore.

There is a great deal being written to-day about diseases of the bursæ. The literature is full of references to acute and chronic inflammation of these sacs, and here and there may be found a description of a tumor of a bursa; syphilis is described involving it as is tuberculosis. The study of the anatomy and development, the pathology and clinical conditions involved in these diseases leaves little more to be added.

In Codman's report we get not only an exhaustive description of the anatomy and development of the subdeltoid bursa, but learn of the changes that may take place in this little known sac. He describes conditions that may be confused with bursal involvement, and the average medical man will be surprised to learn the seriousness of disease of this much overlooked anatomical structure. He will recall many cases of so-called sprain, rheumatism, tuberculosis, neuritis and other conditions about the joints which, in the light of recent investigations by conservative and scientific investigators, are doubtless bursal disease.

Many odd cases in the Johns Hopkins Dispensary called painful shoulders, referred to by Dr. Finney (Johns Hopkins Hosp. Bull., 1894) are doubtless cases of subdeltoid bursitis.

Many cases of inflammation of the prepatellar and olecranon bursæ have been recorded, but little thought has been given to the possibility of similar involvement of many similar sacs throughout the body.

Bursal disease is a common cause of painful conditions about the heel and sole of the foot—many cases having been described in the orthopedic journals. Lund describes three cases of inflammation of the iliopsoas bursa, and Cullen gives the history and an excellent pathological description of a cyst in the pelvis which developed from the iliopsoas bursa which continued its connection with the hip joint.

The numerous bursæ about the hip joint have been the seat of pathological changes as described by Da Costa, Nicaise, Braekett, Thurston, Wietung, Zuelzer, Dueroux and others. Teale gives a case of suppuration of the bursa over the great trochanter and its immitation of hip disease. Braekett, in his article on "Gluteal Bursitis," likewise refers to the simulation of hip joint tuberculosis.

The greatest amount of literature on this subject takes the subdeltoid bursa as the text. Codman, Baer, Painter, Duplay, Bousquet and Kaumheimer cover this field quite thoroughly.

Acute infections due to various micro-organisms are recorded. Kaumheimer describes a purulent pneumococcus involvement following pneumonia. One of Duplay's cases was due to a streptococcus following erysipelas of the hand. Wegner, Heubner and others refer to a mixed infection following syphilis, and Kreuter describes a case of metastatic infection of the subdeltoid bursa from an original osteomyelitis of the femur. The gonococcus and influenza bacillus have likewise played their part in causing acute inflammation of bursæ.

The older writers referred in the main to syphilitic disease as evident in secondary and tertiary lesions. Churchman, writing on this subject, finds twenty-eight such cases in the literature describing them under the name "Luetic Bursopathy of Verneuil." Schuchardt who describes tubercular and syphilitic disease of bursæ in trying to solve the question of fibrin formation or fibrinoid degeneration of rice bodies in hygromas of tendons and bursæ, aids us materially in viewing clearly tubercular disease of bursæ.

Acrel in 1779 first described the "Ganglion Crepitans Acrelii" containing rice bodies which were doubtless tubercular. Dupuytren and Cruveillier likewise described cysts at bursal points containing rice bodies. Dupuytren called them hydatidiform cysts and thought the bodies parasites. Virchow noted them in hygromas and took them for fibrin, but confessed that he afterwards learned they were organized excrescences increasing in size by later gradual fibrin deposits. Although there is a close relationship in anatomy and pathology, between tendon sheaths and bursæ, one must distinguish the cases of tubercular tendo-vaginitis from those of tubercular bursæ for clinical purposes.

There is no doubt that the pathological descriptions of Acrel, Dupuytren and Cruveillier, and the works of Virchow,

Neumann, Riese and others, on fibrin and fibrinoid bodies in tendon-sheath hygromas, apply to the bodies as found in bursal sacs. It is unfortunate that in describing or referring to their cases of tubercular bursæ Brackett, Thurston, Gillette, Ketch, Gibney and Sayre did not give more complete descriptions of their pathology. In none of these cases was reference made to fibrin or fibrinoid bodies. Brackett gave a short clinical history with seven cases of "gluteal bursitis" which he thought were tubercular. In Thurston's case we note that there was calcareous and cheesy material in the contents; but as he simply drained and did not examine the walls of the sac, there is left much of value to be inferred. And as Painter described yellow, cheesy, granular contents and villous enlargements in non-tubercular bursæ, and Cullen described bone, calcareous and cartilaginous masses in a simple cystic bursa, and Kreuter gives a simple subdeltoid bursitis containing cholesterin, fat and brownish fluid, we must still be in some doubt as to the true tubercular character of some of the cases (few as they are) described under the head of "tubercular bursæ."

So far as I can find, the cases of Schuchardt, Riese, Nicaise, Poulet and Vaillard are the only ones which present well-described tubercular bursæ containing rice bodies. They alone described bursal hygromas containing rice bodies. Most of the discussion as to the pathological histology and tubercle bacillus contents of the melon seed or rice bodies in hygromas has been based on work done on those found in connection with tendon-sheaths and joints.

"Tuberculosis of Bursæ" has certainly been not infrequently described, but not as a rule, in connection with rice body contents.

In some of the cases of tubercular bursitis which have been described there has been doubt as to whether the joint or bursa was the primary seat of the disease. In one of our two cases this relationship is a doubtful point. As a rule the question has not been settled. In a few cases—as for example, Thurston's and Brackett's—the rapid healing and disappearance of disease after relieving the bursa of its fluid and draining proves the joint uninvolved.

In some cases it has been demonstrated at operation that there was no connection between bursa and joint by which the disease could have extended from one to the other.

In other cases (Sayre, Lund, Cullen, Gibney and Brackett) a definite communication was demonstrated. From symptoms alone one cannot determine whether the joints are involved. The bursa when inflamed frequently leads one to think it a joint disease. Brackett, speaking of ordinary gluteal bursitis, says it resembles hip disease in its early stages. The X-ray is helpful, as, for example, in one of our cases where there was no evidence of bone lesion connected with the joint. The cloudiness about the joint was evidently due to the bursal contents covering the joint. At operation no communication was seen and incision into the joint showed no involvement. In our second case both joint and bursa were involved at the time of operation, the bursa being a dense mass of fibrous tissue and caseous tubercular material, while the joint showed villous masses of fibrous tissue with lymphoid tubercles in them. Which was the primary seat it is difficult to say. The fact that the disease of the bursa from pathological as well as from clinical data appeared older, would make us believe it to be the original focus of the tuberculosis.

Churchman tabulating twenty-eight cases of "Luetic Bursopathy of Verneuil," says that in only one case was the neighboring joint involved.

Several interesting pathological questions are brought to mind in studying these cases of tuberculosis of bursæ and the literature deals with each one in more or less detail.

The question which has been most actively studied is about the formation of rice bodies. In dealing with this question it has been assumed, and we think quite justly, that the so-called rice bodies including all fibrin or fibrinoid bodies of whatever shape or size, and wherever found, whether in bursæ, tendon-sheaths or joints, belong to the same class. In his work on the subject, Riese includes studies on rice bodies found in all three locations. He goes quite extensively into the history of the knowledge of rice bodies, referring to Acrel as the first, in 1778, to describe real rice bodies; he classified them as atheromatous, comparing them with boiled sago or corn grains. Dupuytren, Brodie, Rokitansky, Virchow, Meckel, von Recklinghausen and others held original views about them.

Cruveillier (1816) and Dupuytren (1839) dealt with them as hydatid cysts. Brodie (1821) considered them coagulated lymph. Rokitansky said they formed from abnormal fluid in the cysts. Virchow first recognized their relation to fibrin in 1846 and originally thought them coagulated masses—clots gradually formed. In 1856 he referred to them as coming from changed intercellular substance by the process of degeneration. Now no one disputes their relation to fibrin. The greater amount of discussion is based on the question—are the fibrin deposits from fluid, or are they changed cellular material, due to a coagulation necrosis, or degeneration of cells? This side of the subject takes up much of Riese's, Nicaise's and Schuchardt's work.

Konig (1884) was the first to recognize their tubercular origin, recognizing at the same time that they were formed by a coagulation necrosis of albuminous material.

Schuchardt acknowledges that rice body hygromas are always tubercular, but does not think that rice bodies wherever found are always due to tubercle bacilli. It would take us too far to describe the pathology of rice bodies in relation to the various structures where they have been found. Some of the most useful literature describing these fibrinoid objects has been found in connection with ganglia and tubercular arthritis. Evans (Am. J. Med. Sc., 1892) wrote the most comprehensive work on the subject in English. Nicaise, Paulet and Vaillard include in their work a combined study of tuberculosis of bursæ and tendons with rice body formations.

Schuchardt made a special study of fibrinoid degeneration of connective tissue under the heading "Tuberculosis and Syphilis of Tendon-sheaths."

We gather from the most enlightened and comprehensive recent writings that the rice bodies are to be considered as

fibrin deposits formed either from coagulable fluid in tubercular sacs, or from a coagulation necrosis of cells or intercellular substance in tubercular tissues.

There is considerable discussion of their mode of formation and relation to the tubercular walls of the containing sac whether bursa, tendon-sheath or joint. After all, we may go back to Virchow's expression of opinion to get at the basis of their formation. This includes some of the best that all express. He says, "I had taken them for clots of fibrin laid down concentrically, but I have since learned that they are organized excrescences. It is possible that they increase in size by gradual fibrin deposits." He thus includes both of the methods of formation, that of an organized material undergoing coagulation necrosis,—the method Schuchardt defends and the credit for proving which he gives to Neumann (Arch. f. mikr. Anat., XVIII, 1880)—and the method of concentric deposition of fibrin as advocated by Nicaise.

These bodies have been described by Nicaise as amorphous and slightly granular bodies with no enveloping membrane. "They are stratified and here and there between the layers are little lacunæ containing bloody granules, refringent bodies like fat or round like leucocytes, but not taking the stain. There may be some remains of connective tissue stained faintly red. . . . . Perfect or incomplete tubercles are found in the sac walls—the very surface shows a varied structure sometimes of connective tissue fibres, again, a thin strip of reddish-brown homogeneous vitreous material under which may be seen a hemorrhagic film and a thin band staining like the rice bodies. . . . . In the center of these one sees vestiges of necrotic cells; at times there is seen a layer of elongated cells, vaguely cylindrical, ending in a mass of granulation tissue beneath. On a level with the surface project some little irregular masses, slightly adherent like beginning rice bodies made of layers doubled on themselves."

Riese says: "The smaller bodies are a meshwork of flaky homogeneous masses running together to form bands taking the fibrin stain. The center is deepest stained. Between single bands there may be seen irregular gaps in which are finely granular masses containing very few leucocytes. At the periphery are some large nuclei (without perceptible protoplasm) and few leucocytes. In some there are seen masses of red blood cells stuck together by fine granules, but no fibrin is present in these."

The presence of tubercle bacilli was shown in the fibrin bodies by all investigators either by staining them or inoculating guinea pigs.

The walls of the containing sac were invariably infiltrated with round, epitheloid and giant cells in varying proportion, and as single or conglomerate or caseated tubercles. There was a varying amount of adherence to surrounding structures. The greatest attention has been paid to the inner lining—this coat showing either caseation or degeneration in lesser degree of cellular material growing as villi.

It was with the desire to decide whether or not these villi were the origin of the rice bodies that Riese, Nicaise, Poulet and Vaillard, and Schuchardt did such extensive work.

Riese and Schuchardt laid more stress on the coagulation necrosis of this surface material as being the point of origin of the rice bodies, while Nicaise seemed to find fibrin deposits or curled masses to account for their origin.

Reinhardt deals with an entirely different condition of the bursa caused by tuberculosis—"Primary Sclerosing Tuberculosis." It is analogous to the second case I describe.

He noticed about the trochanteric bursæ a number of fibrous nodules. These were thick and of a grayish color going suddenly over into the surrounding tissue. In them were seen little pinkish-gray areas 1 mm. in size. Microscopically they were dense connective tissue infiltrated by small round cells in areas; some fat was included. The connective tissue fibers were thick, interwoven and parallel. Some cells were elongated, some were more protoplasmic and stellate. The intima of the vessels was thickened and typical tubercles were seen near the perivascular infiltrated parts—consisting of giant cells of Langhans type, surrounded by epitheloid and round cells and leucocytes. Some areas were composed almost entirely of giant cells; some nodes showed central necrosis with broken down leucocytes or granular material.

Reinhardt records six cases like this and refers to their resemblance to fibroma and syphilitic gummata. The cases are in every respect like that of the prepatellar bursa described by me.

It is interesting to note in this place the varying form in which tuberculosis affects tissues. Reinhardt refers to the French authors, Poncet more especially, who wrote about "sclerosing tuberculosis due to a fibrous diathesis following finished tubercular processes." Ducroux, one of Poncet's followers, described a series of cases of tuberculosis of a "serous bursa" between the scapula and the chest wall which occasioned crepitus and friction sounds. "It is due to a chronic inflammation of a loose cellular tissue (a kind of spread out serous bursa)." He incidentally referred to Poncet's ideas about tuberculous rheumatism where specific anatomic lesions were wanting. He says, "This same condition occurred in tendons, bursæ, cellular organs and all tissues. Some of these cases might be called tubercular rheumatism."

We see in the two cases presented by me typical examples of the two types of tubercular involvement of bursæ described by these writers. They agree with them in all particulars, both in symptoms and pathology.

The condition develops insidiously, sometimes requiring years before the patient considers it worth while to consult a surgeon. He may think it due to rheumatism or a sprain. Examination of the part does not necessarily elicit pain or considerable disability of the part involved until late. There is usually muscle atrophy more or less limited to the parts immediately surrounding the involved bursa; in my cases the deltoid muscle alone showed atrophy.

X-ray examination showed nothing specific by which a diagnosis could be made in either case.

In one case the crepitus of masses in the bulging area was significant, whereas in the case of the prepatellar bursa there was nothing but a dense circumscribed projecting mass which

could have been gummatous quite as well. It is interesting to note that in the shoulder case there was no involvement of the joint, whereas in the prepatellar involvement there were tubercular villi of long standing in the knee joint.

The main interest centers about the pathology of the cases—one representing the type of rice-body formation in a tubercular bursa, the other a chronic sclerosing tubercular process.

Case I.—J. F., white male, age 22 years. Admitted to the Hebrew Hospital, July 26, 1909, complaining of pain at and loss of function of the right shoulder.

Family History.—Good. No tuberculosis.

Past History.—He has always been strong and healthy, never sick in bed in his life.

Present Illness.—For about three years his right shoulder has been stiff on getting up in the morning; this would wear off after he had worked awhile. For the past three months it has been painful all the time. He cannot work because of the pain. It is more painful on motion. The pain is sharp, lancinating in character.

Physical examination shows fullness of the right shoulder, more apparent over the coracoid process, and crepitus under palpating fingers in front of the joint. Tenderness localized at the acromion process. He cannot raise the arm nor place it behind him because of pain. His grip is as strong with the right as with the left hand. He allows the arm to hang helpless by his side.

Measurements:

Right axilla over acromion	15½ in.
Left axilla over acromion	16 in.
Right biceps	10 in.
Left biceps	10½ in.
Right biceps (above)	9¾ in.
Left biceps (above)	10¼ in.

July 29. X-ray shows rarefication over the tuberosity of the humerus and slight roughening here as well as at the upper portion of the glenoid fossa. Joint, negative.

July 29. Two milligrams tuberculin were injected subcutaneously, to which he reacted locally, focally and generally. There was swelling, tenderness and redness at sight of injection, pain the following day at the shoulder, and the temperature rose from 97.3° F. to 100° F.

Aug. 2. Operation, under ether: Incision from the acromion process outwards and downwards toward the deltoid insertion three inches long, through the deltoid muscle exposing a thick gray sac; this was easily exposed by blunt dissection anteriorly, but owing to adhesions about the tuberosity of the humerus and difficulty in getting the sac away above the coraco-acromial ligament, the sac was incised, when about 400 multifacetted bodies flattened against one another shot out, together with a thin serous fluid. The sac was now removed without difficulty. An incision was made into the joint at the point of greatest adhesion near the greater tuberosity; the joint was normal. The bone too was normal. The cartilaginous tip of the acromion process appearing translucent and soft, a longitudinal section 1.5 cm. long, was removed for examination. The muscle was sewed with a continuous cat-gut suture. Skin closed with continuous subcutaneous silkworm gut suture. A small wick of iodoform introduced; arm bandaged with Velpeau bandage, with a Gillette pad in the axilla.

Aug. 5. First dressing: Iodoform drain removed, wound dry.

Aug. 19. Patient discharged healed *per primam.*

Sept. 8. Patient readmitted, complaining of pain in his shoulder and a small sinus at the region of the acromion process in the line of incision. An X-ray was taken showing the joint negative—osteophytes are evident about the tuberosity of the humerus where an exploratory operation was done at the time of excising the bursa.

The sinus was treated and closed by September 22. He was discharged September 29 with arm in a sling, Gillette pad in axilla.

The patient was treated off and on for fistulæ which formed about the site of the old operation—one forming posterior to the axilla at the apex of the axillary fold. One formed about the junction of the outer and middle third of the clavicle and one inch below it.

Jan. 24, 1910. While treating the sinuses it was noted that he was coughing and an examination for admission to the Jewish Consumptive Home at Reisterstown showed both apices of the lungs to be involved by tuberculosis. He was sent to the home, where I treated him. He was discharged much improved both as regards his lungs and shoulder. He then went to the country and returned in excellent condition.

Oct. 15, 1910. The sinuses are all closed and the patient who has been using the arm off and on since the operation is now constantly using it. The muscles over the joint have not recovered their tone, but the biceps reacts strongly and is not atrophied.

Pathological Description of the Case.

The sac containing about 400 grayish-white translucent bodies pressed into multiform shapes resembling in size and shape facetted gall stones, was 11 x 6 x 3 cm. in size, elongated oval in shape. Its wall varied in thickness from 3 mm. to 1 5/10 cm., was firm, homogeneous and gray in color with pinkish areas throughout. At its uppermost end under the acromion process it was a dense fibrous tongue of tissue wedged against the softened cartilaginous tip of the acromion process. Its inner lining was softer and of yellowish color, but smooth for the greater part, trabeculated here and there. The rice bodies stuck firmly in this meshwork. There were some few nodular areas, but no villous processes could be picked off until deeper in the walls of the sac. These nodular areas resembled the material of the rice bodies but were softer. The sac was in layers 2 mm. thick at the outermost shell. The outermost walls were hemorrhagic and shreddy, but dense connective tissue existed where the sac was adherent. The contents consisted of round, oval and facetted bodies varying from to 2 to 8 mm. in size; these were so densely packed that some force was required to separate numbers of them. Many of them fitted snugly depressions and pockets among the trabeculæ in parts of the wall of the sac. They were of a grayish-white color and translucent appearance—not very firm, the center being darker and softer than the periphery. They consisted of layers, the outermost being 2 mm. thick. These could be picked apart, easily cut, so that free hand sections were made for staining for fibrin and tubercle bacilli while yet fresh. There were some elongated shreds resembling the above but softer and more shreddy and darker, resembling blood-stained fibrin. Microscopic examination showed the bodies to be a granular loculated material staining with Weigert's fibrin stain and showing flakes, granules and strands. Traces of nuclei were faintly stained here and there. Tubercle bacilli were found with the Ziehl-Neelsen's stain.

In acetic acid this material swelled showing a fenestrated

CASE I.—BEFORE OPERATION.

CASE II.—TUBERCULAR BURSITIS.

CASE II.

CASE I.—AFTER OPERATION.

TUBERCULAR BURSA WITH FIBRIN BODIES.

appearance. The bone from the tuberosity of the humerus was rather porous but showed no cellular infiltration or hemorrhage. The bone cells and lacunæ showed no pathological alteration.

The softened tip of the acromion process showed mucoid degeneration of the cartilage cells, some of them appearing in stellate forms.

Sections were made from many portions of the sac through its entire thickness. It showed typical tuberculosis and of varying histological structure, dense fibrous tissue containing areas of small round cells, small round cells and epithelioid cells, sometimes giant cells, sometimes caseation with these or areas where caseation was the only microscopic change seen. In places there were single and conglomerate tubercles. Many vessels were occluded by two or three giant cells with few epithelioid cells, some small round cells about them. Frequently a gradation could be traced from the dense fibrous outer structure to the cellular, infiltrated, softer inner wall, to degenerated non-staining cells and lastly to a lining of granular or flaky non-staining material, with apparent lines of cleavage traversing it in some sections.

Where adhesions held the sac to surrounding parts near the tuberosity of the humerus the outermost tissue was very much congested and hemorrhagic, but was fairly well distinguished from the sac by the latter's dense structure, and its containing rounded spaces lined by tubercular giant cells. There were no infiltrating round cells or giant cells in this adherent wall.

Case II.—The second case is one where there was associated tuberculosis of the neighboring joint.

C. R., white male, age 24 years. Admitted to the Hebrew Hospital, February 18, 1910, complaining of swelling over the prepatellar bursa and swollen, painful left knee.

Family History.—Father died of Bright's disease. A brother died of tuberculosis. Wife healthy, two sons healthy.

Past History.—No serious illness until 20 years of age, when he had typhoid fever. Never had venereal infection. He later had pleurisy.

Present Illness.—Patient has had the swelling (nodular mass) over his patella for several years; it has not bothered him. He now complains of pain in the knee-joint which he traces to a fall November 27, 1909, when he struck the left knee; two days later the knee began to be painful. The pain was so great at night that he could not sleep. He was treated in the Dispensary of the Hebrew Hospital, getting relief, so that the pain was intermittent. He could move the leg all right, except when it locked on occasions.

A physical examination showed the patient to be well developed and normal except for a tubercular focus in the apex of right lung.

Note of Resident Physician.—The left thigh and leg are smaller than the right. The left knee is thickened and warmer than the right, and tender on both inner and outer sides. There is a lump over the patella the size of a hickory nut, elastic to the touch, freely movable under the skin. The left leg may be flexed on the thigh to a little more than a right angle.

The tuberculin test was positive. There were 8800 leucocytes. Differential blood count:

Polymorphonuclears	57.00%
Small mononuclears	37.50
Large mononuclears	1.50
Transitionals	2.50
Eosinophiles	1.50

An X-ray examination showed evidence of foreign material in the joint and the symptoms pointing to such a condition, he was operated upon on February 19, 1910.

Operation.—A long incision (4 inches) on the inner side, to include the prepatellar bursa, was made, and a shorter one along the outer side of the knee-joint.

The capsule was incised and a number of tags of a pinkish-yellow color were removed. The largest of these 2½ cm. in length and pedicled, was loose in the joint. After closing the capsule with a continuous silk suture, the prepatellar bursa, a dense fibrous mass, was excised. The skin wounds were closed with subcutaneous silk-worm gut sutures, and the limb put in a plaster of Paris cast.

The wound did badly—the prepatellar area healed by granulation but the joint and surrounding tissues became involved in an active tubercular process until amputation of the limb was necessitated on August 11, 1910.

The mass removed from the prepatellar region, measuring 4 x 3 x 2 cm., was solid, fibrous, glistening white material which cut with difficulty, but showed softer grayish areas here and there. It faded gradually into the surrounding fat.

Microscopically it was a dense fibrous mass containing islands of small round cells, epithelioid and giant cells, and some caseous areas. It extended into the fat tissue by dense fibrous bands.

The tags removed from the joint showed masses of round and epithelioid cells and areas of degeneration.

The examination after operation of the muscle, glands and necrotic material from the joint showed active tuberculosis mostly epithelioid, giant and small round cells, with many polymorphonuclear leucocytes infiltrating the softer parts. Many conglomerate tubercles were present.

Summary.

It will be seen that our cases correspond exactly to the types of tuberculosis of bursæ containing rice bodies, described, as in the first case, by Nicaise, Poulet and Vaillard, Leriche and Rhenter, and Schuchardt, and in the second case to the sclerosing type described by Reinhardt and Ducroux.

We can add nothing new to their work either in connection with the clinical findings or pathology. We trust that by calling attention to the rarity of the condition and giving references to the best that has been written in regard to this subject, besides adding our own confirmation of their findings, we may aid others in studying tuberculosis of bursæ.

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A DEVICE TO AID IN KEEPING THE PATIENT DRY AFTER A SUPRAPUBIC CYSTOSTOMY.

By George Walker, M. D.,
Associate in Surgery, Johns Hopkins University, Baltimore, Md.

The device consists of a pure gum rubber sheet, 1 yard square, with a round hole in the center 6 to 8 inches in diameter. The material is similar to that used by dentists.

The sheet is laid on the patient immediately next to the skin so that the opening falls over the suprapubic wound. The usual amount of absorbent gauze is then laid on the wound, and the borders of the sheet are folded in, covering the gauze completely. The sheet with the enclosed gauze is held in place by an ordinary abdominal binder or Scultetus bandage.

By this arrangement whenever the gauze becomes saturated the fluid drains into the dependent portion of the sheet, where it collects and allows almost no leakage for several hours, during which time the patient's bed and clothing are kept dry.

When properly adjusted the sheet is also of very material aid in protecting the clothing when the patient is in a wheel chair or walking about.

A large opening in the rubber is necessary in order to supply a sufficient absorptive surface for the gauze.

This arrangement has been found to work admirably with some patients, keeping them almost dry; for others, owing to the configuration of the abdomen, it will prove less satisfactory, but in all cases it undoubtedly adds to the general comfort.

IN MEMORIAM.

DR. CHRISTIAN A. HERTER.[1]

Christian Archibald Herter was born in Glenville, Connecticut, September 3, 1865, and died at his home in New York City, December 5, 1910, in the forty-sixth year of his age. His early education, partly by private teachers and at the Columbia Grammar School, was largely influenced and directed by his father, a man of wide culture and scholarly attainments. He was graduated Doctor of Medicine at the College of Physicians and Surgeons (Columbia University) in 1885. He pursued graduate professional studies at the Johns Hopkins University, and later in Germany and France. He was Visiting Physician to the New York City Hospital from 1894 to 1904, Professor of Pathological Chemistry at the University and Bellevue Hospital Medical College from 1898 to 1903, and since 1903 Professor of Pharmacology and Therapeutics at the College of Physicians and Surgeons. He was a member of the Board of Referees appointed by the President of the United States to act as advisers to the Department of Agriculture in the enforcement of the National Food and Drugs Act.

With the incorporation of the Rockefeller Institute for Medical Research in June, 1901, Dr. Herter, who had been active and influential in the preliminary conferences, became a member of the Board of Directors, and served for a number of years as its Treasurer. His death marks the first break in the membership of the Board as originally constituted.

From the date of his graduation in medicine, Dr. Herter's life was one of singular devotion to the pursuit and advancement of scientific medicine—a devotion ever increasing and burning never more brightly than during the last years of a progressive and wasting nervous affection. To this life-work he brought the intellectual qualifications of the successful investigator of nature, good training, industry and enthusiasm. With the scientific temperament was joined, in unusual degree, the imaginative and artistic, in music especially, his accomplishments being those of a virtuoso.

Opportunities for scientific research Dr. Herter created largely for himself, by constructing on the top floor of his house a well-equipped laboratory for experimental, pathological, bacteriological and chemical investigations, and by securing the services and co-operation of able assistants and collaborators. From this private laboratory have issued during the last fifteen years numerous and valuable contributions.

Dr. Herter was a prolific contributor to medical science, his published articles and books numbering not less than seventy, and covering a wide range of activity. His earliest scientific interest related to diseases of the nervous system, his first publications in this field appearing in 1888, followed in 1889 by his valuable study of experimental myelitis, and later by several articles of pathological and clinical interest, and by the publication in 1892, of the first edition of his text-book on "The Diagnosis of Diseases of the Nervous System." After this period his work lay more and more in the domains of experimental pathology, and especially of pathological chemistry, being concerned with problems of metabolism, of the formation of gall stones, of glycosuria, of anæmia and toxæmia and of infantilism; and in the later years particularly with the study of the intestinal bacterial flora and intestinal putrefaction. His lectures on "Chemical Pathology in its Relation to Practical Medicine," published in 1902, met a most favorable reception. He approached pathological problems with broad biological, and even philosophical interest.

Dr. Herter's services to American medicine are not to be measured solely by his published contributions, valuable as these are. The example and influence of his personality and of the ideals which he represented made strongly for higher professional standards and for the wider recognition and cultivation of medical science. The lectureships which Dr. Herter, in association with Mrs. Herter, established upon wise and generous foundations at the Johns Hopkins Medical School and the University and Bellevue Hospital Medical College serve a most useful purpose in the promotion of scientific medicine.

It was mainly through Dr. Herter's instrumentality and generous support that the "Journal of Biological Chemistry" was established in 1905, and he was also active in the organization, in 1908, of the American Society of Biological Chemists.

Biological chemistry in this country owes a large debt to Dr. Herter, whose death after a little more than two decades of fruitful activity is indeed a severe loss to American medicine.

Dr. Herter's services were of great help in the planning and development of the Rockefeller Institute. After the opening last September of the hospital of the Institute, to which he had been appointed physician, and which owes much in its conception and general character as a research hospital to the time and thought devoted to it by him, Dr. Herter began to make use of the opportunities there offered, which seemed to be the fulfilment of his dreams for study of the problems of disease as presented by the living patient. The zeal and ardor with which he entered upon this work seemed to his colleagues wonderful, and indeed heroic, in view of the increasing and distressing physical infirmities of the last weeks of his life.

The memory of Christian Archibald Herter will continue to be a stimulating influence to be perpetuated and cherished as an example of good scientific work, of generous material aid in the promotion of medical science, of devotion to the best interests of his profession, of fine culture, loyalty of character, broad humanity and high idealism.

[1] Extract from Minute prepared for the Rockefeller Institute for Medical Research by Dr. W. H. Welch.

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NOTES ON NEW BOOKS.

Œdema: A Study of the Physiology and the Pathology of Water Absorption by the Living Organism. The Nathan Lewis Hatfield Prize Essay of the College of Physicians of Philadelphia, by MARTIN H. FISCHER, Professor of Pathology in the Oakland School of Medicine, Oakland, Cal. (*New York: John Wilcy & Sons. London: Chapman & Hall. 1910.*)

Physiology and pathology depend so much upon the fundamental sciences that any attempt to bring them into closer relations must be welcomed by the medical reader. Dr. Fischer has considered the occurrence of œdema from the physico-chemical standpoint as merely one phase of the whole problem of the transfer of water into and out of the tissue cells, and this in turn as only an expression of the amount of water which the proteids of the tissues can absorb under the conditions in which they are placcd. Under this conception conditions which favor absorption by colloids cause the tissues to take up water, while the conditions which lessen the absorption cause the tissues already saturated with water to excrete it.

His fundamental experiment is as follows: "If one leg of an ordinary frog or tree frog or a toad is ligated just above the knee as tightly as possible, so that the ligature shuts off not only the venous flow but also the arterial, and the animal is then placed in sufficient distilled water to cover the legs, the ligated leg develops an intense œdema, while the unligated one remains normal"—in spite of the fact that no circulation can take place through the blood vessels. "*It is clear,*" he states, "*that the cause of œdema resides in the tissues themselves and that these become œdematous not because water is forced into them, but because changes take place in them whereby they are enabled to absorb water from any available source.* In the case of the experiments on toads and frogs this available source is the water contained in the dishes in which the animals are kept. In clinical cases of œdema, this is found in the fluids which pass through or about a tissue." The immediate cause for this change in the properties of the tissues he supposes to be the production of acids, especially of lactic acid, in the tissues, which Araki has shown results whenever there is lack of oxygen.

Exactly the same experiments were described in 1898 by Dr. Jacques Loeb,[1] of whom Dr. Fischer was a pupil. In this paper Dr. Loeb demonstrated the formation of organic acids in the muscle after ligation, ascribed it to the lack of oxygen, and demonstrated that the muscle tissue took up water in proportion to the acid formation. It is unfortunate that Dr. Fischer, we believe unintentionally, has failed to do justice to the work of his illustrious predecessor and has described many repeated experiments in a manner which leads the casual reader to regard them as original. In interpretation, however, Dr. Fischer differs somewhat from Dr. Loeb, since he disregards entirely the rôles of cell or capillary walls and is unwilling to ascribe even a secondary rôle to filtration as a factor in the genesis of œdema.

Dr. Fischer gives a good discussion of Overton's theory that the surface of cells is made up of lipoid substances (such as lecithin, cholesterin, protogen, cerebrin, etc.) which in their properties as solvents are unlike ether or the fatty oils, and that only such substances penetrate the cells as are soluble in or miscible with these lipoids. Dr. Fischer himself regards the proteids of the surface as more important than the lipoids. He gives some interesting physico-chemical experiments to show that while acids facilitate the imbibition of water by gelatin, fibrin, muscle and sheep's eyes, this process is inhibited by various salts and inhibited most by the tartrates and citrates. He very ingeniously injects acids into gelatine plates with a syringe and shows that "wheals" are thus formed about the injection very similar to those due to insect bites (in which the poison is also an acid).

Dr. Fischer goes on to apply his theoretical conclusions to various clinical conditions, notably to glaucoma. He regards glaucoma as due to swelling of the colloids of the eyeball, similar to what occurs when the eyeball is placed in acid. He believes that it is independent of circulatory phenomena. Acting upon this suggestion the author and H. G. Thomas have used instillations of sodium citrate and tartrate in the treatment of glaucoma, and claim that the intraocular tension was diminished thereby. This theory of glaucoma has been criticised recently by E. v. Knape[2] and awaits confirmation.

Dr. Fischer also cites some interesting experiments on the removal of experimental œdemas in frogs by immersion in sodium citrate solutions, and states that Dr. John D. Long has successfully treated the œdema about inflamed joints by injection of sodium citrate—a result which the author has been able to duplicate by local injections of sodium citrate in œdematous tissues of cardiac disease and nephritis. These observations, though few in number, are of practical importance. If confirmed by further observation they may lead to a distinct advance in the treatment of œdema.

The rest of the book deals with œdema of the lungs, turgor, plasmolysis and plasmoptysis, the secretion of urine by the kidney and hæmolysis. The two latter sections are interesting and contain some suggestive experiments.

The style of the author is, in the main, clear and interesting. The book is well printed, and although italics are used somewhat freely they enable the casual reader to get some idea of the author's conclusions without a careful perusal of the text. The figures and curves are good and add to the clearness of the subject matter.

The book as a whole contains much and varied information, with numerous references to suggestive articles. In spite of a good deal of special pleading it furnishes interesting reading even where one cannot agree with the author's views.

A. D. H.

Vicious Circles in Disease. By JAMIESON B. HURRY, M. A., M. D. (Cantab.), ex-President Reading Pathological Society. (*London: J. and A. Churchill, 1911.*)

In the fight against almost every disease the efforts of the physician may be baffled by the establishment of vicious circles, in which one factor of the malady gives rise to and perpetuates another. Nevertheless, though a foreknowledge of the vicious circles that may be encountered may be almost as essential as the diagnosis and the initial treatment, clear-cut descriptions of vicious circles are rarely met with in textbooks; and in most of the latter only a small percentage of existing vicious circles are mentioned.

In this book Dr. Hurry has given the first systematic collection of the vicious circles which occur in medical practice and has illustrated their mode of production with excellent graphic representations, which add much to the clearness of the text. He has also collected a large number of instances in which the circles may be broken or reversed by therapeutic means. Such a book does not aim to supplant the text-book and is bound in a certain degree to sacrifice accuracy to brevity, but it cannot fail to furnish helpful suggestions to both student and practitioner, and merits the perusal of both.

A. D. H.

[1] Physiologische Untersuchungen ueber Ionenwirkungen, IV, Zur Theorie des Œdems. Arch. f. d. ges. Physiol., Bonn, 1898, lxxi, 469.

[2] Skand. Arch. f. Physiol., 1910, xxiii, 162.

Text-Book of Massage. By L. L. DESPARD, Member and Examiner Incorporated Society of Trained Masscuses. Price, $4.00. (*London: Henry Frowde and Hodder & Stoughton, 1911.*) *Oxford University Press.*

Miss Despard has written an excellent chapter on massage, and it is a pity the entire volume is not given to this alone, but the first 175 pages are devoted to the anatomy of the human body, copiously illustrated with pictures more suited to students of advanced anatomy than to those who are anxious to learn massage; only 75 pages are given to the most important part of the work, which is completed by two cursory chapters on bandages and electricity in conjunction with massage. The photographs to show the different methods of giving massage are most satisfactory, and this text-book, even though we feel it is not well balanced, is to be recommended without restriction to students of this art.

History of Medicine. By MAX NEUBURGER, Professor of Medical History in the Imperial University of Vienna. Translated by Ernest Playfair, M. B., M. R. C. P. In two volumes. Vol. I. Crown, 4to. (*London: Oxford University Press, 1910.*)

To the Germans especially we are deeply indebted for critical and exhaustive study of the records of the past. Their matchless patience, their tireless industry and perseverance, their vast linguistic resources and their judicial temperament, have borne rich harvests of literature. In no department have the results been more conspicuous and important than in the field of medical history, and the work before us affords striking proof of the fact. As Professor Osler points out in the Preface written by him, "The output in Germany of works and monographs representing scholarship of the first class is equal to the rest of the world put together," and the immediate future is rich in promise of still more important contributions. The libraries of Europe are being ransacked for new and revised Greek and Latin texts, which are to be published under the auspices of the Imperial Academy of Berlin and the Institute at the University of Leipzig for the study of the history of medicine founded by the late Professor Puschmann. Meanwhile, we can feast on the treasures set before us in Gurlt's monumental *Geschichte der Chirurgie* and the more recent encyclopedic general history designed by Puschmann, and on his early death taken up and completed by his pupils, Professors Neuburger and Pagel, the latter of Berlin (1902-5).

It was to be expected that the elaborate researches undertaken in these works, especially the latter, by so many distinguished scholars, would lead to the production of a convenient manual embodying all that is essential for the student and the general reader, and that has been accomplished by Professor Neuburger in the work before us in a manner that gives no occasion for anything but praise.

The subject is treated in a fresh and animated style that holds the reader's interest from beginning to end. The general narrative is given in large type while the details are filled in with small type, an arrangement that is helpful and affords pleasing variety and relief. The principle of evolution is fully and constantly recognized; yet progress has been far from uniform or continuous. "The history of medicine is no calm, unbroken evolution, but a series of advances by fits and starts, with interruptions of subjective influence and with change of scene. . . . . Many of the finest intellects squandered their energies upon grotesque error which obscured many valuable half-truths. . . . . The most brilliant speculative systems barred the way to progress and *a priori* deduction, not reconsidered in the light of experience, served but to lead medicine astray."

Full justice is done to the new discoveries made in Mesopotamia and Egypt, the science of pick and shovel and the elucidation of cuneiform inscriptions having opened to us in the former case the unexpected civilization of the Sumerians, Babylonians and Assyrians, reaching back beyond 3000 B. C., while the famous Ebers and Bugsch papyri in the latter furnish records of little less antiquity. Yet the beginning is not yet, for back of these was an already protracted period of development, of which Babylon and Nineveh were only the most historically important products.

Egypt has left deeper traces upon the memory of man than Babylon, a fact which is to be attributed to its intimate relations with the nations bordering on the Mediterranean, to Jewish and Greek literature, especially the Bible and Homer, and to the striking and mysterious remains found in the Valley of the Nile. But the records already brought to light, according to Neuburger, hardly substantiate the superiority of the Egyptians over their Eastern predecessors, either in religion or science, while their claim to originality is becoming more and more doubtful.

It is interesting to learn that there are traces of auscultation in the Ebers papyrus; also that hygiene and prophylaxis occupied so predominant a status and had reached so astonishing a development among the ancient Egyptians. But other nations, as the Indians, led by their religious views, appear to have paid scarcely less attention to it. Neuburger concludes that it is clear that Egypt exercised a powerful influence upon the social hygiene of the Jews, upon Greek medicine and through these upon the development of mankind.

One of the finest sections of the entire work is that dealing with "the matchless collection of writings bearing the name of Hippocrates, greatest of all physicians," to whom the School of Cos owes its transcendant title to fame. But it can no longer be maintained that these writings emanated exclusively from Hippocrates; "in the light of searching criticism they are nothing but the motley, heterogeneous output of generations, the intellectual product of many thinkers, whose individual voices only chance has united to form a single chorus by no means invariably harmonious." Yet there is an individuality permeating them which is traceable to the strong influence of a single dominating personality. This personality looms up grandly but dimly through the ages, like a stream with many springs, vivifying and inexhaustible; admired by all, really understood by few, imitated by many, equalled by none, the master of medicine for all time. We may conclude that the Hoppocratic ideal will live, unfettered by doctrines, to remotest ages.

Not inferior in breadth and clearness is the section relating to Galen and his system—"the climax of scientific effort in ancient medicine."

One is struck with the frequency with which the author inculcates caution as to final judgment. This applies not only to the medicine of the early periods, the Babylonic-Assyrian and Egyptian, but also to that of later times, as the Arabian. To quote in the latter case: "Since the manuscripts which have been so far investigated bear only a small proportion to the extent of the original literature, and considering the possibility, by no means unprecedented, that research may bring forth surprising discoveries, it follows that we are not at present in a position to express a final opinion upon the achievements of Arabic medicine in detail." This is the true historic attitude of a mind ever open to the reception of new truths and ready to be convinced.

The author's fairness is everywhere manifest and even when forced to condemn he finds something to praise. He seeks to judge events from a contemporary standpoint which is the only way to do justice to them. This is particularly seen in dealing with the Methodists, whose most shining adherent was the celebrated gynecologist, Soranus of Ephesus.

In conclusion, we will only say that we have found nothing to criticise in this incomparable work which will stand for many years to come as the leading text-book on the subject.

The work of the author has been ably seconded by Ernest Playfair, who has given us a spirited and scholarly translation, in which he has steered clear of the German idiom, a thing so difficult to do in translations from that language.

We shall await with deep interest the appearance of the second volume dealing with a much larger subject and one more closely connected with present-day medicine.

The style of the book needs no comment, as the excellence of the Oxford publications is well known.

E. F. C.

BOOKS RECEIVED.

Interne Klinik der bösartigen Neubildungen der Bauchorgane. Von Priv.-Doz. Dr. Rudolf Schmidt. Mit einer Farbigen Tafel. 1911. 8vo. 355 pages. Urban & Schwarzenberg, Berlin, Wien; Rebman Company, New York.

Diseases of the Anus, Rectum, and Sigmoid. By Samuel T. Earle, M. D. With 152 illustrations in the text. 1911. 8vo. 476 pages. J. B. Lippincott Company, Philadelphia and London.

The Care and Training of Children. By Le Grand Kerr, M. D. 1910. 12°. 233 pages. Funk & Wagnalls Company, New York and London.

The Dawn of the Health Age. By Benjamin Moore, M. A., D. Sc., M. R. C. S., L. R. C. P. 1911. 12°. 204 pages. J. & A. Churchill, London; The Liverpool Booksellers' Co., Ltd., Liverpool; P. Blakiston's Son & Co., Philadelphia.

"Salvarsan" or 606 (Dioxy-Diamino-Arsenobenzol) Its Chemistry, Pharmacy and Therapeutics. By W. Harrison Martindale, Ph. D. Marburg, F. C. S., and W. Wynn Westcott, M. B., Lond., D. P. H., H. M.'s Coroner for North-East London. 1911. 8vo. 77 pages. Paul B. Hoeber, New York.

Bismuth Paste in Chronic Suppurations. Its Diagnostic Importance and Therapeutic Value. By Emil G. Beck, M. D. With an Introduction by Carl Beck, M. D., and a Chapter on the Application of Bismuth Paste in the Treatment of Chronic Suppuration of the Nasal Accessory Sinuses and the Ear, by Joseph C. Beck, M. D. With eighty-one engravings, nine diagrammatic illustrations, and a colored plate. 1910. 8vo. 237 pages. C. V. Mosby Company, St. Louis.

The Treatment of Syphilis by the Ehrlich-Hata Remedy (Dioxy-Diamido-Arsenobenzol). A Compilation of the Published Observations. By Dr. Johannes Bresler. Second edition, much enlarged, with the portraits of Ehrlich and Schaudinn. Translated by Dr. M. D. Eder. With an Abstract of the Most Recent Papers. 1910. 12°. 122 pages. Rebman Limited, London; Rebman Company, New York.

Accidental Injuries to Workmen. With Reference to Workmen's Compensation Act, 1906. By H. Norman Barnett, F. R. C. S. With Article on Injuries to the Organs of Special Sense. By Cecil E. Shaw, M. A., M. Ch., M. D., and Legal Introduction by Thomas J. Campbell, M. A., LL. B. [1909.] 8vo. 376 pages. Rebman Company, New York.

Remedial Gymnastics for Heart Affections Used at Bad-Nauheim. Being a translation of "Die Gymnastik der Herzleidenden" von Dr. Med. Julius Hofmann und Dr. Med. Ludwig Pöhlman. By John George Garcon, M. D. Edin., &c. With fifty-one full-page illustrations and diagrams. 1911. 8vo. 128 pages. Paul B. Hoeber, New York.

Makers of Man. A Study of Human Initiative. By Charles J. Whitby, M. D. (Cantab.) With forty-seven half-tone and other plates. [1910.] 8vo. 424 pages. Rebman Company, New York.

Golden Rules of Ophthalmic Practice. By Gustavus Hartridge, F. R. C. S. "Golden Rules" Series. No. VII. Fifth Edition. [1910.] 32°. 72 pages. John Wright & Sons Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

The Principles of Pathology. By J. George Adami, M. A., M. D., LL. D., F. R. S., and Albert G. Nicholls, M. A., M. D., D. Sc., F. R. S. (Can.). Volume II. Systemic Pathology. Second edition, revised and enlarged with 301 engravings and 15 plates. 1911. 8vo. 1160 pages. Lea & Febiger, Philadelphia and New York.

Handbook of Treatment for Diseases of the Eye. (Ophthalmic Therapeutics). By Curt Adam. With a Preface by Prof. von Michel. Translated from the second German edition (1910) by William George Sym, M. D., F. R. C. S. Ed., and E. M. Lithgow, M. B., F. R. C. S. Ed. With thirty-six illustrations. [1910.] 12°. 264 pages. Rebman Company, New York.

Plastic and Cosmetic Surgery. By Frederick Strange Kolle, M. D. With one colored plate and five hundred and twenty-two illustrations in text. 1911. 8vo. 511 pages. D. Appleton and Company, New York and London.

Modern Treatment. The Management of Disease with Medicinal and Non-Medicinal Remedies. In Contributions by American and Foreign Authorities. Edited by Hobart Amory Hare, M. D., assisted by H. R. M. Landis, M. D. In Two Volumes. Volume II. Illustrated. [1911.] 8vo. 900 pages. Lea & Febiger, Philadelphia and New York.

A Handbook of Practical Treatment. By Many Writers. Edited by John H. Musser, M. D., LL. D., and A. O. J. Kelly, A. M., M. D. Volume I. 1911. 8vo. 909 pages. W. B. Saunders Company, Philadelphia and London.

Blakiston's ? Quiz-Compends ? Compend of Gynecology. By William Hughes Wells, M. D. Fourth edition, revised and enlarged with 153 illustrations. 1911. 12°. 290 pages. P. Blakiston's Son & Co., Philadelphia.

Diseases of the Joints and Spine. By Howard Marsh, M. A., M. C. Cantab., F. R. C. S. New and enlarged edition thoroughly revised by the author and C. Gordon Watson, F. R. C. S. With 4 colored and 8 black-and-white plates, and upwards of 100 illustrations in the text. 1910. 12°. 632 pages. Chicago Medical Book Company, Chicago.

Atlas of Microscopic Diagnosis in Gynecology. With Preface and Explanatory Text by Dr. Rudolf Jolly, Priv. Doc. Only authorized English translation by P. W. Shedd, M. D. With 52 lithographs in color and 2 textual figures. [1911.] 4to. 192 pages. Rebman Company, New York.

A Manual of Physical Diagnosis. By Brefney Rolph O'Reilly, M. D., C. M. (F. T. M. C., Toronto; M. R. C. S., Eng.; L. R. C. P., Lond.). With 6 plates and 49 other illustrations. 1911. 12°. 369 pages. P. Blakiston's Son & Co., Philadelphia.

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CARBOHYDRATE TOLERANCE AND THE POSTERIOR LOBE OF THE HYPOPHYSIS CEREBRI.[1]

AN EXPERIMENTAL AND CLINICAL STUDY.

By Emil Goetsch, Harvey Cushing and Conrad Jacobson.

(*From the Johns Hopkins Hospital and the Hunterian Laboratory of Experimental Medicine.*)

SUBJECT HEADINGS.

I. Introduction.
  Presupposition of a lowered assimilation limit.
II. Methods followed in the experiments.
III. Protocols of hypophysectomies, demonstrating:
  Early post-operative lowering of carbohydrate tolerance.
  Ultimate overtolerance for carbohydrates.
  The relation of this overtolerance to posterior lobe deficiency.
  Summary of experimental results.
IV. The assimilation limit in clinical cases of dyspituitarism.
  Ultimate increase of tolerance in acromegaly and gigantism.
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  Effect of posterior lobe extracts in lowering the assimilation limit.
  Relation of the high assimilation limit to adiposity.
  Therapeutic dosage.
V. Influence of ductless glands in general and hypophysis in particular on tolerance for sugars.
  Historical summary. Acromegaly and diabetes.
  Explanation of the discrepancies in past studies.
VI. Résumé and conclusions.

I. Introduction.

In the series of 100 experimentally hypophysectomized animals observed in this laboratory in 1908-1909,[2] certain unlooked for symptoms were found to occur in a number of the animals surviving for long periods after a partial removal of the gland. They were interpreted as manifestations of pituitary insufficiency and laid—erroneously as we now believe—solely at the door of anterior lobe defects. The most noteworthy of these symptoms was a tendency toward adiposity, coupled with genital dystrophy; the females failed to go into heat and sexual indifference or impotence was apparent in the males, some of whom showed a definite testicular atrophy.

A histological study of the ductless glands of this series of animals demonstrated the occurrence of alterations in all of them as a consequence of the primary hypophyseal lesion. The conjecture was a natural one that possibly some of the clinical symptoms which had been observed were due to these secondary changes in other members of the ductless gland series, rather than that they were a primary outcome of the pituitary deficiency itself—an indirect rather than a direct effect, in other words. For example, it was conjectured that the adiposity might be due to defective testicular or ovarian secretion and thus be akin to the adiposity following castration; that the transient glycosuria which was observed in a few instances might be due to a hyperplasia of the thyroid or adrenals, or to a state of lowered activity of the islets of Langerhans, or even perhaps of the pancreatic acini themselves.

With this suggestion in mind it was proposed among other objects to devote our 1909-1910 series to a more careful histological scrutiny of the changes in these other glands. We directed our attention particularly to the alterations which occur in the pancreas and its islets, with results which will appear in

[1] Presented by Dr. Cushing at the meeting of the American Physiological Society held in New Haven, December, 1910.

[2] S. J. Crowe, Harvey Cushing and John Homans: Experimental hypophysectomy, The Johns Hopkins Hosp. Bull., 1910, XXI, 127-169.

a subsequent paper. These studies naturally led us into an investigation of the carbohydrate tolerance of the hypophyseetomized animals, and our observations in this direction form the basis of this present communication, in which reference will also be made to certain clinical applications of our findings.

In the earlier series (1908-1909) as recorded by Crowe, Cushing and Homans, though polyuria was commonly observed, the immediate post-operative presence of a reducing substance in the urine had been noted in a few instances only. It was naturally ascribed to the anæsthetic. The animals in our present series (1909-1910) were observed with greater care in this respect, and it was learned that an early and spontaneous glycosuria might be anticipated in the majority of the animals. This was particularly true of those subjected to the operation for total removal, whether or not the gland proved subsequently to have been extracted in its entirety; for it is in this procedure that the hypophyseal stalk is manipulated and crushed in a particular way.

As this post-operative glycosuria proves to be transient, it is a natural supposition that many cases which would have shown a reducing substance were overlooked in the series of the previous year, since the routine of examining the first voided specimen was not followed. Furthermore, in view of the marked polyuria which usually occurs, if the first specimen, with its definite reducing properties, is allowed to become diluted with the total day's amount the early and transient appearance of a reducing substance may readily escape notice on a casual examination of the mixed 24-hour specimen—another possible source of error.

It must be said, however, that in a number of the animals in our present series a trace of the reducing substance often persisted for a day or two, the early typical reduction of Fehling's solution gradually fading to a mere greenish-yellow discoloration—referred to as an "atypical reduction" and probably not due to dextrose. The reducing body of the earlier specimens, it may be added, gives a positive yeast fermentation test and is dextro-rotatory.

After a fragmentary hypophysectomy this spontaneous post-operative glycosuria was found to occur with less regularity, though as our charts will show, a temporarily lowered assimilation limit may be expected even under these circumstances. This fact suggested that the character of the glandular manipulations was the essential element in the production of the glycosuria, rather than the operative method of approaching the gland or the administration of the anæsthetic: for the surgical procedure and the duration of the performance are practically the same whether the object be a partial or a total removal. The chief difference between the two operations lies in the manner of treating the stalk, for in the partial removals this structure need not, and should not, be damaged by the glandular manipulations. On the other hand, in the extirpation destined to be total, after freeing the vascular dural attachment of the posterior lobe, the infundibular attachment of the dangling gland is pinched off in the forceps as high up as possible, so that as little as may be of the pars intermedia is left adhering to the infundibular stalk and tuber cinerium. If the manipulations have been successful the isolated gland is then lifted out intact.

Needless to say, in all of the animals the urine was examined previous to the operation, and it may be noted that in the large number of dogs subjected to hypophysectomy in our present series no instance of pre-existing glycosuria has been observed. In order to test the relation of the anæsthetic to the problem, a number of animals of the average size and age employed in this series were anæsthetized with ether for corresponding periods without the subsequent appearance of a reducing body in the urine. For further control, a few typical operations were carried to the point of free exposure of the gland, but without subjecting the structure itself to any manipulation. These animals also showed no reducing substance in the urine.

These primary observations, disclosing the frequent occurrence of glycosuria immediately after a total hypophysectomy, led us to conjecture that the assimilation limit in these animals would subsequently be found to be altered, and it was presupposed—erroneously as events proved—that a permanently lowered carbohydrate tolerance would be demonstrable. This furthermore is the view which has been the basis apparently of all previous investigations.

With this preconception, a primary test was made upon two young dogs of approximately the same size and age, one being hypophysectomized, the other used as a control. A day or two after the spontaneous post-operative glycosuria of the former puppy had disappeared, a diet of white bread in equal amounts was given to the two animals. The reducing substance promptly reappeared in the urine of the animal subjected to operation, whereas the urine of the control had no reducing properties. Contrary to our expectation, however, this lowered assimilation limit shown by the hypophyseetomized animal did not persist, and after a number of days even forced feeding with white bread failed to produce glycosuria in either animal. It was evident that the carbohydrate tolerance, distinctly lowered during the early post-operative period, had again increased after an interval of a few days. Whether the former assimilation limit had merely been regained or whether an actual increase in tolerance had become established could not, of course, be determined by such a crude experiment.

Having in mind, therefore, that the post-operative spontaneous glycosuria bore a definite relation to the surgical manipulations of the gland and that the brief period of carbohydrate intolerance was followed by a re-establishment of tolerance at least to the normal, it was determined to test these points more systematically.

II. Conduct of Experiments.

Healthy young dogs, averaging about one year of age and usually of the fox-terrier type, were chosen as subjects. Each animal was confined in a carefully constructed metabolism cage for a number of days before the operation, on a diet consisting of 125 to 150 gms. of lean ground beef. This was boiled to obviate the intestinal disturbances engendered by the feeding

of raw meat over long periods. On this standard diet the animals, during the preliminary tests to establish their normal sugar tolerance, remained in good condition with normally formed stools, and uncontaminated urine could be obtained.

In performing the hypophysectomy we have followed the same operative methods practiced in the Hunterian Laboratory during the past two or three years and fully described by Crowe, Cushing and Homans. The surgical difficulties associated with this delicate procedure may with experience be so completely overcome as to enable one to remove, in the average case, the entire structure, the anterior or the posterior lobe, or practically any desired proportion of either lobe. After one has learned to free the posterior dural attachment of the gland at the point of entry for the vessels to the para nervosa,[3] the dislocation and removal of this separate lobule, together with its epithelial investment is one of the simplest of the various forms of glandular mutilation. However, there need rarely be any uncertainty at the time of operation as to the degree of success of the attempted measure, whatever it may be. In the entire series, nevertheless, not only have the fragments removed at operation been sectioned, but in every case serial sections have been made of the interpeduncular block of tissue removed post mortem. This block should include the base of the third ventricle, the optic chiasm and the entire contents of the sella turcica, together with its dural lining. Only in this way is it possible to establish beyond equivocation not only the size but the state of functional activity of the glandular fragment which has been left.

In the carbohydrate assimilation tests definite weighed amounts of cane sugar dissolved in warm water were administered by a stomach tube. In all cases the normal tolerance of the individual animals was approximately established by a series of determinations previous to the hypophysectomy, and the post-operative tolerance was established by the same method after varying intervals of time.[4] For a number of reasons we have in most cases preferred to work on the basis of tolerance for carbohydrate ingested rather than given intravenously. It gave us a better estimate of the power of absorption, destruction and storage of sugar than could have been acquired had the carbohydrate been thrown in large amounts directly into the circulation. Furthermore, the animals were less inconvenienced and fewer abnormal factors were introduced than would have been the case with such frequent intravenous injections as the tests would have required. After one or two experiences tractable animals accept the stomach tube without resistance.

Saccharose was chosen—despite its being a somewhat more complex body than glucose—partly for the reason that if the animals drooled into the cages after the administration of the sugar there would be no danger of contamination of the urine by a reducing substance—a possible risk in the case of glucose administered by mouth. Needless to say, the cages were thoroughly and frequently cleaned, and in case one of the animals acquired diarrhœa during the progress of the experiments sugar feeding was interrupted and all specimens of urine under the suspicion of contamination by converted saccharose which had been carried through the intestinal canal and ineffectually screened out, were discarded. However, the chance of error on this score with cane sugar feeding seems very slight; for in a few animals afflicted with diarrhœa, causing an obvious contamination of the urine, the dextrose tests were always negative provided the amount of sugar administered had been below the assimilation limit.

In some animals in the late post-operative stages, when the assimilation limit became very high, the large amount of carbohydrate would not always be completely retained by the stomach. If any sugar was regurgitated, however under such circumstances the urine would betray this fact by its high specific gravity and content of mucus and food particles and the findings could be disregarded. Scrupulous observance of these precautions should eliminate the possible sources of error associated with this manner of making the tests.

However, for purposes of control, tests were made in certain cases with the intravenous injection of from 20 to 25 per cent glucose solution.[5] In a number of instances, furthermore, extracts of posterior lobe, of anterior lobe and of thyroid gland were administered hypodermically, intravenously or by mouth, simultaneously with the sugar feeding, with the results to be recorded below.

III. Protocols of Experiments.

At the outset of our investigations it was unknown to us whether the obvious disturbances of carbohydrate metabolism were associated with the activity of the pituitary body as a whole or with the function of one or another of its anatomical subdivisions. We were somewhat prejudiced in favor of the anterior lobe, in view of the stress laid on this portion of the gland in the earlier studies from this laboratory. Thus in practically all of the cases of spontaneous post-operative glycosuria and in the instance of white bread feeding related above, we were dealing with animals subjected to a complete or to a nearly complete extirpation of the entire gland—animals, in other words, in whom the characteristic symptoms of acute glandular deficiency (cachexia hypophyseopriva) were likely to appear after intervals varying from two to three weeks. As the carbohydrate tolerance was first systematically studied in connection with operations of this type the results may be presented at the outset, for though they are far less striking than in the case of the longer lived animals they nevertheless show points of interest.

Four of our observations (Nos. 60, 63, 57, 66) belong in this group. In two of them the normal tolerance was established for cane sugar by mouth, and in the other two for glu-

[3] Dandy and Goetsch: The blood supply of the pituitary body. *Am. J. Anat.*, 1910, XI, p. 137.

[4] Had we been cognizant when these studies were undertaken of the more refined methods of quantitative determination of the sugar output in the urine we would have been spared the tedium of these repeated tests to establish the tolerance.

[5] In order to prevent the introduction of an unnecessarily large amount of fluid into the circulation, the more concentrated solutions were used as the assimilation limit increased.

cose intravenously, before the hypophysectomy. All four animals promptly recovered from the operation, but it was necessary to sacrifice them in from two to three weeks owing to the onset of symptoms of cachexia. Nevertheless the post-operative observations made in this interval showed in two cases a transient spontaneous glycosuria, in three cases a temporary lowering of the assimilation limit and in three a slight increase in the tolerance before death even in this short period. This restoration of the normal tolerance and a final slight increase over the former assimilation limit was shown for the intravenous as well as for the intraoral method of sugar administration. For the purpose of comparing these two methods both of them were employed in one individual (No. 58) in a subsequent group.

A. Observations on the changes of the assimilation limit for cane sugar by mouth and glucose intravenously in animals deprived of nearly the entire gland.

The first four protocols therefore will record the observations made upon animals subjected to a complete or nearly complete glandular extirpation. Needless to say they have been shorn of practically all data unrelated to the subject in question.

No. 60.—(Series of 1909-10.) *Primary lowering of tolerance for cane sugar by mouth during week after operation. Subsequent rise to normal. Tests interrupted by attack of distemper with onset of cachexia hypophyseopriva on 23d day.* (Table I.)

TABLE I.—TESTS OF TOLERANCE FOR CANE SUGAR BY MOUTH IN No. 60.

Date.	Grams of cane sugar given.	Urine.					
		Amt.	Sp.Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
May 17	0	160	1032	0	0		
" 18	70	240	1050	0	0		
" 20	80	240	1020	+	+	+	
" 21	90	150	1022	+	+	+	
" 28	Nearly complete hypophyseetomy; small fragment of anterior lobe remaining.						
" 29	0	110	1038	0	0		
" 30	0	120	1028	0	0		
" 31	60	90	1044	+	+		
June 1	60	240	1060	+	+	+	
" 2	50	30 (?)	....	0	0		
" 3	70	300	1060+	+	+	+	
" 4	70	140	1040	+	+	+	.6%
" 6	70	200	1046	0	0		
" 7	80	150	1050	+	+	+	.3%
" 8	0	150	1030	0	0		
" 10	0	200	1040	0	0		

A healthy male, 6.6 kilo, adult fox terrier about one year of age. Kept in metabolism cage for four days prior to operation to determine normal assimilation for saccharose by mouth (cf. Chart I). Tolerance established between 70 and 80 gms.

May 28. Operation.—Removal of posterior lobe and practically entire anterior lobe; gland fragmented in removal. Operative estimate a "nearly total" hypophysectomy. A small tag, supposedly of anterior lobe, left adherent at infundibular stalk.

May 29.—No post-operative polyuria or glycosuria.

May 31-June 10.—Establishment of post-operative tolerance at about 20 gms. below normal on the third and fourth days. Subsequent rise to 80 gms., the normal tolerance. Rapid accession of body weight from 6.6 kilos to 7.4 kilos during period of sugar ingestion.

June 13.—Symptoms of distemper led to a discontinuance of further tests.

June 20.—Distemper followed by usual manifestations of ensuing cachexia. Animal sacrificed.

Autopsy.—Apparently an almost total removal. A small granule, which might be glandular substance visible at the base of the stalk. No recognizable posterior or anterior lobe. Nothing of special note in the gross examination of the other organs. Infundibular block, including contents of sella turcica, preserved as usual for serial sectioning.

Histological.—The two fragments removed at operation proved upon microscopical examination to be the intact posterior lobe and a large portion, if not all, of the anterior lobe.

The autopsy specimen showed on serial sections a few cells of the intermediate lobe type adnerent to the infundibular floor. No anterior or posterior lobe seen—in short, a more complete extirpation than had been intended.

Comment.—The observation is not a particularly valuable one. The operative intent had been to leave just enough of the anterior lobe to preserve the life of the animal, a total removal of this lobe being incompatible with life, as has been shown. Attention has been called to the fact that an animal under these circumstances is particularly susceptible to infections or to intestinal derangements, which are apt to precipitate the acute symptoms of excessive glandular deficiency shown by a fall in temperature, tremors, arching of the back, a slowed respiration and ultimate coma. The distemper which occurred on the 26th day interrupted the tests and provoked these terminal symptoms.

It will be noted that no spontaneous post-operative glycosuria and polyuria were observed. This is so exceptional as to make us fear that a first specimen may have been lost or unrecorded. A temporarily lowered assimilation limit, however, was apparent, for on the third day 60 gms. of saccharose produced glycosuria, whereas 80 gms. had been required before the operation. By the ninth day the original sugar tolerance was practically regained, 80 gms. again giving a slight reduction. Attention is drawn to the increment in body weight of nearly 12 per cent during the sugar feeding period of 10 days.

No. 63.—(Series of 1909-10.) *An increase of tolerance for saccharose by mouth seven days after a "nearly total" hypophysectomy. Attempted reduction of tolerance by the hypodermic in-*

TABLE II.—TESTS OF TOLERANCE FOR CANE SUGAR BY MOUTH IN No. 63.

Date.	Grams of cane sugar given.	Urine.					
		Amt.	Sp.Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
May 31	0	310	1048	0			
June 1	60	150	1050	0			
" 2	70	340	1030	0			
" 3	80	260	1020	+	+		
" 5	80	280	1015	+ slight	+	+	.3%
" 6	0	180	1040	0	0		
" 7	Nearly complete hypophyseetomy; small fragment of anterior lobe remaining.						
" 8	0	400	1020	0	0		
" 9	0	440	1010	0	0		
" 10	0	120	1040	0	0		
" 11	0	140	1022	0	0		
" 12	70	10 (?)	....	0	0		
" 13	80	210	1028	0	0		
" 14	90	110	1022	+	+	+ slight.	.2%
" 16	90	150	1034	0	0		
" 17	100	210	1032	0	0		
" 18	110	180	1028	0	0		
" 19	120	330	1020	+	+		

jection of posterior lobe extract causes regurgitation. Symptoms of cachexia hypophyseopriva after 30 days. (Table II.)

A healthy male, 9.1 kilo, fox terrier, about six months of age and apparently full-grown. Observed for six days previous to operation. *Normal tolerance* to cane sugar feeding established at something below 80 gms.

June 7. Operation.—A nearly total removal of the gland. No surgical difficulties. Prompt recovery from the anæsthetic. No post-operative complications.

June 8-9.—A moderate polyuria without demonstrable glycosuria.

June 12.—Animal in perfect condition. Feeding tests begun with 70 gms.; negative.

June 14.—Glycosuria first induced by 90 gms., more than 10 above the established normal.

June 16-19.—The tolerance increased in this interval (cf. Chart II) to something below 120 gms., 40 gms. above the established normal.

June 21.—One hundred grams of sugar with a coincident hypodermic injection of posterior lobe (0.5 gm.) caused immediate vomiting, whereas this amount had been readily taken before.

June 24.—A repetition of the experience of June 21: prompt vomiting of 80 gms. On June 26 a similar experience with 80 gms.

June 30.—Subnormal temperature with onset of symptoms of cachexia. Animal sacrificed.

Autopsy.—The naked eye examination of the floor of the third ventricle and of the sella turcica disclosed no definite glandular structure. The other organs showed nothing of note beyond a beginning pneumonia and a mediastinal abscess.

Histological.—Microscopical examination of the tissue extirpated at operation showed it to consist of the entire, unbroken, posterior lobe and a large fragment of anterior lobe. Serial sections of the autopsy material disclosed a remaining small group of viable anterior lobe cells and the usual tag of pars intermedia—in other words, a "nearly total" extirpation.

Comment.—This second case merely serves as another instance of an increase in the tolerance to cane sugar by mouth (80 to 120 gms.) after removal of nearly the entire hypophysis. It also illustrates the tendency of posterior lobe injection to produce vomiting of ingested sugars. Otherwise the record is of no especial interest. It is another exception to the general rule regarding a post-operative spontaneous glycosuria. Symptoms of cachexia hypophyseopriva doubtless supervened on the intrathoracic infection of obscure origin. A viable fragment of anterior lobe was left, sufficient in size to have preserved life under ordinary conditions.

No. 57.—(Series of 1909-10.) *Determination of tolerance for intravenous glucose solutions after nearly total hypophysectomy. Primary fall followed by a secondary rise exceeding the normal. Reduction of the increased tolerance by the hypodermic administration of posterior lobe extract. Onset of cachexia hypophyseopriva on the 12th day.* (Table III.)

June 3.—A healthy, 7.6 kilo, fox-terrier bitch, about 7 months of age, apparently full-grown, was observed for six days previous to operation, on the usual standard diet. The animal's *normal tolerance* was established at approximately 6 gms. of glucose administered intravenously in 20 per cent solution into the external jugular.

June 9. Operation.—Extirpation considered as practically total. (Fig. 1.) Prompt recovery from the anæsthetic. Animal returned to metabolism cage. No operative or post-operative complications of any kind.

TABLE III.—TESTS OF TOLERANCE FOR INTRAVENOUS INJECTION OF GLUCOSE IN NO. 57.

Date.	Cubic centimeters of fluid injected.	Grams of glucose injected.	Urine. Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
June 3	0	0	130	1022	0	0		
" 4	25	5	200	1040	0	0		
" 5	35	7	50	1048	+	+	+	1%
			100	1030	0	0	0	0
" 6	30	6	100	...	+ sl.	+ sl.	+ sl.	.2%
" 7	0	0	120	1050	0	0		
" 8	30	6	230	1030	+ sl.	+	+	.2%
	Nearly total hypophysectomy.							
" 9	0	0	400	1015	+	+	+ sl.	.2%
" 10	0	0	200	1014	0	0		
" 11	0	0	200	1030	0	0		
" 12	20	4	60	1040	+	+	+	.3%
" 13	17.5	3.5	90	1050	0	0		
" 14	25	5	100	1042	0	0		
" 15	25 c. c. 25% sol.	6.25	120	1040	0	0		
" 16	0	0	140	1042	0	0		
" 17	30	7.5	100	1044	0	0		
" 18	35	8.75	110	1034	0	0		
" 19	40	10	70	1042	+	+	+	1.1%
" 20	25 cc. + 0.05 gm. post. lobe hypo.	6.25	60	1044	+	+	+	.2%

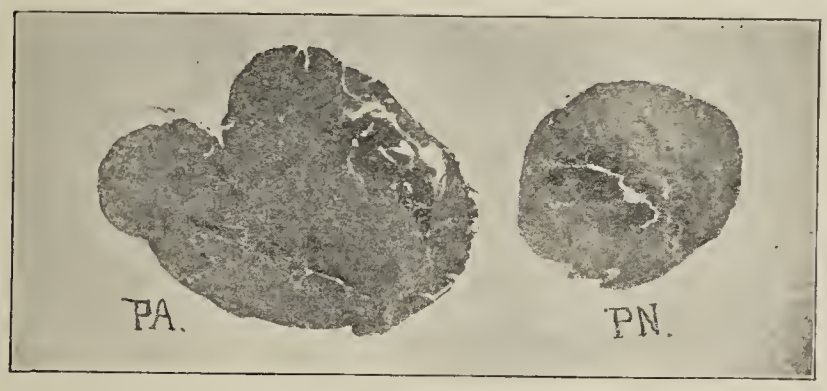

FIG. 1.—Nine diameters magnification of posterior and anterior lobe of No. 57, removed at operation. Bensley; 5 μ; iron-hæmatoxylin. Pars nervosa (P N) dislocated from its bed in anterior lobe (P A) during removal.

June 9-10.—Slight post-operative polyuria with spontaneous glycosuria on first specimens voided.

June 10-11.—Animal in perfect condition. Polyuria and glycosuria have subsided.

June 12.—Four gms. of glucose intravenously caused a reappearance of the glycosuria—an amount 2 gms. below the established pre-operative normal.

June 12-20.—Intravenous tolerance for glucose gradually increased during this period, until on June 18 intravenous injection of 8.75 gms. of glucose did not cause glycosuria, but 10 gms. on the following day gave a positive reduction.

Post-operative tolerance therefore estimated at slightly below 10 gms.—4 gms. over the pre-operative normal.

June 20.—A smaller dose of carbohydrate, namely, 6.25 gms. of glucose, given coincidently with a hypodermic injection of .05 gm. of posterior lobe extract caused glycosuria.

June 23.—The animal was sacrificed owing to the onset of symptoms of cachexia hypophyseopriva.

Autopsy.—The naked eye examination of the base of the brain and sella turcica confirmed the operation as a nearly total removal of the gland. No apparent fragments of either lobe. Nothing noteworthy on gross examination of other organs. Tissues preserved and sectioned in the usual manner.

Histological.—Serial sections of the infundibular region reveal merely a small residual fragment of pars intermedia adjacent to

the infundibular stalk (Fig. 2), confirming the practical totality of the extirpation.

Comment.—In this animal an earlier attempt to determine the carbohydrate tolerance by mouth had been abandoned, owing to persistent regurgitation, and recourse was had to the injection methods. The case demonstrates that the tolerance for glucose intravenously behaves in precisely the same manner as that for cane sugar by mouth. In other words, there is a lowered assimilation limit for the first few days after operation and a subsequent increase over the normal as determined before operation.

The protocol clearly indicates that in these states of increased sugar tolerance the coincident hypodermic injection of a small amount of posterior lobe extract may lower the tolerance at least for glucose administered intravenously and cause a temporary glycosuria. Attention may be called to the fact that the injection of posterior lobe extracts does not serve to

FIG. 2.—Nine diameters magnification of one of the series from the interpeduncular block of No. 57. Section No. 25; 5 μ; Helly; H and E. Showing small fragment of stalk (S) with few adherent pars intermedia cells (P I), organized clot (C), vessels and sellar dura below (D), commissure (D C).

ward off states of threatened cachexia hypophyseopriva, as does the administration of anterior lobe or whole gland extracts. If the whole gland had been used not only might these terminal symptoms have been at least postponed, but the lowering of the sugar assimilation limit would have been shown as well.

No. 66.—(Series of 1909-10.) *Relative tolerance for intravenous glucose solutions before and after a practically complete hypophysectomy. Demonstration of post-operative increase in tolerance which could be lowered by the coincident hypodermic injection of posterior lobe extract. Acute symptoms of apituitarism on the 12th day.* (Table IV.)

June 4.—A healthy, 6.9 kilo, dog, about one year of age, was confined in a metabolism cage on the usual diet for six days previous to operation. The *normal tolerance* for 20 per cent glucose solutions introduced into the external jugular was established at about 7.5 gms.

June 10. Operation.—Usual technique. A supposedly total extirpation. Gland removed intact. Prompt recovery from the anæsthetic. No post-operative complications.

TABLE IV.—TESTS OF TOLERANCE FOR INTRAVENOUS INJECTION OF GLUCOSE IN NO. 66.

Date.	Cubic centimeters of fluid injected.	Grams of glucose injected.	Urine. Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
June 4	0	0	140	1030	0			
" 5	0	0						
" 6	25	5	90	1026	0	0		
			190	1026	0	0		
" 7	35	7	120	1022	0	0		
" 8	40	8	140	1032	+	+	+	.6%
" 9	37.5	7.5	120	1040	+	+	+ sl.	.5%
			150	1020	0	0		
" 10	0	0	120	1042	0	0		
	Total hypophysectomy.							
" 11	0	0	2700	1006	1st spec +	+	+	
					0	0	0	
" 12	0	0	700	Some feces.	0	0		
" 13	0	0	640	1012	0	0		
" 14	0	0	720	1008	0	0		
" 15	0	0	6 (?)	1040	0	0		
" 16	0	0	720	1008	0	0		
" 17	0	0	510	1010	0	0		
" 18			450	feces.	0	0		
" 19			410	feces.	0	0		
" 20	40	8	360	1022	0	0		
" 21	40	10	520	1020	0	0		
" 22	45	11.25	320	1016	0	0		
" 23	40 + 0.5 gm. post. lobe hypo.	10	120	1020	+	+	*	Slight R.

* Not determined.

June 11.—A marked polyuria (2700 cc. in 24 hours), with spontaneous glycosuria showing only in the first voided specimen.

June 12-19. No injections were made during this interval.

June 20.—Injections resumed. Eight grams negative.

June 21.—Intravenous injection of 10 gms. of glucose in 25 per cent solution—2½ gms. above the pre-operative tolerance established on June 9—produced no glycosuria.

June 22.—An injection of 11.25 gms. was likewise negative, showing that the *post-operative tolerance* was at least more than 3.75 gms. above the previously established normal.

June 23.—The intravenous administration of 10 gms. with a coincident hypodermic injection of .05 gm. of posterior lobe extract, produces glycosuria.

June 24.—Animal ill; slow pulse and respiration with subnormal temperature evidence the onset of symptoms of hypophyseal cachexia. Sacrificed.

Autopsy.—A total removal, judging from naked eye appearances of the base of the brain. No gross lesions in the other organs.

Histological.—The tissue removed at operation proved to be the major portion if not the entire gland. The autopsy specimen showed the presence of an intermediate lobe fragment, and the entire absence of the posterior lobe and characteristic cells of the anterior lobe.

Comment.—This is a second illustration of increase in the intravenous tolerance to glucose. In twelve days the tolerance rose to more than 3.75 gms. over the normal determined before operation, an increase of 50 per cent. Here again an injection of posterior lobe extract served temporarily to lower the acquired degree of overtoleranee.

B. Observations on sugar tolerance after deprivation of a portion of the anterior lobe alone.

We have seen that operative removal of the anterior and posterior lobes together may cause a primary fall and subsequent rise above the normal in the assimilation limit for

sugars. Obviously the next step would be to determine whether this acquired capacity for storing carbohydrates depends upon the loss of either subdivision of the gland singly, or whether it is related to the cessation of function in the structure as a whole.

In the earlier studies from this laboratory particular stress was laid upon the physiological importance of the pars anterior. As an outcome of some of the earlier experiments in the present series we became aware that our predecessors had attributed the post-operative disturbances which they observed too exclusively to this subdivision of the gland. Their attention had at first been directed more particularly to the acute disturbances leading up to cachexia hypophyseopriva—a state which supervenes on the loss of the entire gland—and this abrupt upsetting of the physiological equilibrium they had properly ascribed to deficiency of the anterior lobe, for posterior lobe extirpation seemed in no way incompatible with the maintenance of life.

So far, however, as the acquired tolerance for carbohydrates is concerned a deficiency of the anterior lobe seems to play, at least relatively, a very insignificant rôle. This is shown, firstly, in negative fashion by the failure of animals deprived of a portion of the anterior lobe alone to acquire a high post-operative tolerance; and, secondly, in more positive fashion by the fact that an acquired overtolerance can be lowered much more effectually by the injection of posterior lobe extracts than by the injection of extracts or emulsions of the pars anterior. Indeed such positive reductions in the assimilation limit as actually followed injections of anterior lobe extracts we are inclined to attribute to some fragments of pars intermedia that may easily have clung to the anterior lobe during the mechanical separation of the two glandular subdivisions in the process of preparing the separate extracts.

It will be seen in the following experiment that a partial removal of the pars anterior led to the usual immediate post-operative lowering of tolerance due to the operative manipulations. However, there was no subsequent acquirement of over-tolerance, such as seems to be inevitable when the posterior lobe has been removed, whether alone or coincidently with some of the pars anterior.

No. 50a.—(Series of 1909-1910.) *Determination of the assimilation limit for cane sugar by mouth before and after removal of a fragment of the anterior lobe. Posterior lobe remaining, though traumatized. Effect of hypodermic administration of posterior lobe extract on the established tolerance.* (Table V.)

April 15.—A healthy, 8.5 kilo, adult fox-terrier bitch. *Normal tolerance* for saccharose administered by mouth estimated at about 110 gms. (i. e. between 110 and 115 gms.). It was found that this normal assimilation limit could be reduced by the coincident injection of small amounts of posterior lobe extract. Thus glycosuria would occur with only 70 gms. of sugar given with one-twentieth of a gm. of posterior lobe extract.

May 17. Operation.—Removal of a considerable fragment, possibly one-third, of the anterior lobe. The posterior lobe was slightly traumatized but was not removed. The animal made a prompt recovery from the anæsthetic and operation, and remained well during the succeeding days of observation. The first specimen voided after operation showed a slight glycosuria.

May 17-21.—Slight post-operative polyuria. Animal in excellent condition.

May 22.—120 gms. of saccharose by mouth showed a reduction.

May 24.—110 gms. gave a mere trace of reducing substance. Tolerance about the same as before operation (cf. Table V, April 19 and 28).

May 27.—A hypodermic injection of .05 gm. of posterior lobe extract with 70 gms. of saccharose gave the same degree of glycosuria as on May 5 before the operation. Animal sacrificed.

Autopsy.—Naked eye examination of the base of the brain shows the hypophyseal stalk and much of the gland itself intact. The interpeduncular block and the dura of the sella turcica were dissected out as usual in one piece and fixed for sectioning.

Histological.—The small fragment removed at operation proved to be pars anterior alone: no pars intermedia included. Serial sections of the interpeduncular block removed at autopsy showed a normal intact posterior lobe and a large fragment of anterior lobe.

TABLE V.—TESTS OF TOLERANCE FOR CANE SUGAR BY MOUTH IN NO. 50A.

Date.	Grams of cane sugar given.	Injection of glandular extracts.	Urine.				
			Amt.	Sp.Gr.	Fehling.	Fermentation.	Polariscope.
Apr. 15	50	....	250	1035	0	0	0
" 16	65	.....	350	1010	0	0	0
" 17	80	.....	450	1035	0	0	0
" 18	100	.....	300	1020	0	0	0
" 19	115	.....	260	1030	+	+	1.3% D. R.
" 21	105	.....	400	1040	0	0	0
" 28	110	.....	500	1030	0	0	0
May 4	90	.05 gm. post lobe hypo.	700	1030	+	+	1.5% D. R.
" 5	70	.05 gm. post. lobe hypo.			+	+	1.0% D. R.
" 17	Partial hypophysectomy: fragment of anterior lobe alone removed.						
" 17	.....	....	1st spec.		+	+	1.5% D. R.
" 18	.....	.....	860	1006	0	0	0
" 19	....	.....	850	1005	0	0	0
" 20	....	....	850	1008	0	0	0
" 21	.....	.....	600	1007	0	0	0
" 22	120	.....	600	1030	+	+	0.7% D. R.
" 24	110	.....	700	1030	+ susp.	0	0
" 26	50	.05 gm. post. lobe hypo.	400	1010	0	0	0
" 27	70	.05 gm. post. lobe hypo.	300	1030	+	+	1.0% D. R.

Comment.—Though not a particularly conclusive observation, nevertheless the protocol, when compared with those of the following group, shows that a pure anterior lobe defect without a concomitant posterior lobe lesion need produce little alteration in the carbohydrate assimilation limit. The injection of posterior lobe extract had the same action after operation as before—namely, the reduction of the tolerance from about 110 gms. to something below 70 gms.

This is one of the few cases where a partial removal of the gland without intentional contusion of the stalk caused a transient post-operative glycosuria, sugar being detected in only the first specimen voided after operation.

C. Observations on the sugar tolerance of animals deprived of the posterior lobe and a fragment of the pars anterior, enough of this lobe being left for the maintenance of life.

Removal of practically the entire gland has been shown to produce a transient lowering and subsequent rise in tolerance in the short interval before the onset of the acute terminal symptoms of glandular deficiency. Removal of a portion of

the anterior lobe alone in a single case showed no subsequent increase in tolerance.

As the two following protocols will show the removal of the posterior lobe, together with only a fragment of anterior lobe—a condition not incompatible with the long maintenance of life—causes the same primary lowering of tolerance and the subsequent rise above the previously established normal.

In the second of these experiments (No. 35), the animal was kept under observation for some five months, and the persistence of the established rise in the assimilation limit is well shown, even though a portion of the pancreas had been removed before the hypophysectomy.

No. 59.—(Series of 1909-10.) *Determination of the assimilation for saccharose administered by mouth after a partial hypophysectomy including the posterior and a fragment of the anterior lobe. The usual primary post-operative decrease in tolerance was followed by a secondary rise exceeding the normal. Comparative action of hypodermic injections of posterior and of anterior lobe extracts in reducing the acquired tolerance.* (Table VI.)

TABLE VI.—TESTS OF TOLERANCE FOR CANE SUGAR BY MOUTH IN No. 59.

Date.	Grams of cane sugar given.	Dosage of glandular extract.	Urine.					
			Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
May 17	0	.....	240	1040	0	0		
" 18	60	.....	360					
" 19	70	.....	240	1022	0	0		
" 20	90	.....	210	1020	suspic.		+	
" 21	100	.....	280	1030	suspic.	0	0	
" 22	110	.....	420	1022	+	+	+	
" 24	Hypophysectomy; post. lobe and fragment of ant. lobe removed.							
" 25	0	.....	1750	1008	0	0	0	
" 26	0	.....	2320	1006	0	0		
" 26	110	1st spec.	225		+	+	+	.6%
		2d spec.	40		++		++	2.3%
		3d spec.	610	1010	0	0		
" 27	80	1st spec.	65		+		+	
		2d spec.	425	1008	+		+	.8%
" 28	70	1st spec.	20		+		+	.1%
		2d spec.	260	1022	0		0	
" 29	60	1st spec.	15		+ sl.		+	
		2d spec.	100	1030	0	0		
" 30	50	.....	220	1030	0	0		
" 31	70	.....	170	1040	0	0		
June 1	80	.....	220	1028	0	0		
" 2	100	.....	200	1027	0	0		
" 3	110	.....	170	1030	0	0		
" 4	120	.....	320	1034	0	0		
" 5	130	.....	210	1030	+ sl.	+ sl.	+	1.2%
" 8	130	.....	200	1020	+	+	+	.3%
" 12	130	.....	180	1040	+ sl.	+ sl.		1.2%
" 21	110	.05 gm. post. lobe hypo.	80	1048	+	+	+	1.5%
" 22	100	.05 gm. post. lobe hypo.	150	1040	+	+	+	.7%
" 26	100	.05 gm. ant. lobe hypo.	120	1038	0	0		
" 28	100	.1 gm. ant. lobe hypo.	100	1060+	+ sl.	+ sl.	+	1.1%

A healthy, 7.5 kilo, bitch, about nine months of age. Observed for six days previous to operation, on the usual standard diet. *Normal tolerance* established at about 100 gms. cane sugar by mouth.

May 24. Operation.—Satisfactory exposure of gland. Posterior lobe and left half of anterior lobe removed without apparent stalk injury. No operative complications.

May 25-30.—Marked post-operative polyuria (2320 cc.). No spontaneous glycosuria observed.

May 25-29.—Demonstration of greatly lowered tolerance—namely to 60 gms. or less, approximately 40 gms. below the pre-operative normal limit.

May 30-June 4.—Gradual increase of tolerance to 120 gms.

June 5-12.—Tolerance established at 130 gms. (30 gms. above normal).

June 22.—.05 gm. of posterior lobe extract hypodermically caused glycosuria with 100 gms. of cane sugar.

June 26.—.05 gm. of anterior lobe extract hypodermically caused no glycosuria with 100 gms. of cane sugar.

June 28.—0.1 gm. of anterior lobe extract hypodermically caused glycosuria with 100 gms. cane sugar, double the dose of posterior lobe extract required.

June 29-July 3.—Attempts to compare the effect of posterior lobe extract administered by mouth with the subcutaneous dosage proved ineffectual, as 0.2 gm. caused prompt vomiting of the 100 gms. of saccharose.

July 23.—Dog in good condition. Showing no symptoms of hypophyseal deficiency. Sacrificed. Autopsy conducted as usual.

Histological.—The tissue removed at operation consisted of the intact posterior lobe together with a large fragment of pars anterior. The interpeduncular block removed at autopsy showed a considerable residue of viable anterior lobe together with a small remnant of pars intermedia.

Comment.—There was an unusually high grade of post-operative polyuria in this case, and unfortunately the first voided specimens were not secured and tested for sugar. As the marked diuresis and spontaneous glycosuria usually go hand in hand, both presumably representing the introduction into the circulation of excessive amounts of posterior lobe secretion, a transient glycosuria might have been expected. However, a temporarily lowered tolerance (40 gms. below the normal) was demonstrated even to the sixth day (May 29) after the operation. Had we been making a quantitative study this would have been apparent earlier, namely, on the third day (May 16), when 110 gms. gave an abundant reduction, as it did before the operation. By the 13th day (June 5), the tolerance had risen to 130 gms. (30 gms. above the normal), where it remained about stationary for three days. It may possibly have risen to a higher level subsequently, but no further tests were made unassociated with the injection of extracts.

It can be seen that .05 gm. of posterior lobe extract administered hypodermically served to restore the post-operative tolerance practically to the former pre-operative level of 100 gms. This may therefore possibly represent the degree of secretory insufficiency of the posterior lobe. Double this amount of anterior lobe extract was needed to produce the same effect. However, as we have stated, this tolerance lowering action of pars anterior extract is in all likelihood due in large measure to the almost unavoidable incorporation of some of the pars intermedia in the preparations.

Several attempts were made to estimate the relative amounts of posterior lobe, given by mouth and administered hypodermically, in producing glycosuria with the 100 gm. doses, but the ingestion of the extract invariably caused vomiting of the sugar.

No. 35.—(Series of 1909-10.) *Determination of the assimilation limit for saccharose of an animal deprived of the posterior and a portion of the anterior lobe. Rise in assimilation limit to double the previous normal.* (Table VII.)

With the thought in mind, as indicated in our introductory paragraphs, that the alterations in carbohydrate tolerance might

be associated with changes in pancreatic activity, a number of the earlier animals in the series were subjected to a pancreatectomy, all of the gland but its duodenal attachment being extirpated. In the following case as a result of this operation the usual spontaneous pancreatic glycosuria occurred, but the normal tolerance was soon regained. The hypophysectomy was performed two months later.

December 29, 1909.—A healthy, full-grown, 7.5 kilo, dog, about

TABLE VII.—TESTS OF TOLERANCE FOR SACCHAROSE BY MOUTH IN No. 35.

Date.	Grams of cane sugar given, and dosage of glandular extract.	Urine. Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
Dec. 29	Partial pancreatectomy, duodenal attachment remaining.						
" 30	0	100	1055	+ sl.	+ sl.	+	.35% D. R.
" 31	0	125	1050	0	0		
Jan. 31	50	150	1025	0	0		
Feb. 1	60	200	1030	+		+	.4% (8 gm. 24 hrs.)
" 25	60	120	1035	0	0		
" 26	70	400	1015	0	0		
" 27	80	200	1040	0	0		
" 28	90	200	1040	+	+	+	.5% D. R.
Mar. 1	85	150	1035	0	0		
" 4	Hypophysectomy posterior lobe and large fragment anterior lobe.						
" 4	1st spec.	150	1050	+	+	+	
	2d spec.	600	1018	0	0		
" 5	50	450	1020	0	0		
" 7	70	375	1038	0	0		
" 9	80	400	1035	0	0		
" 11	100	140	1042	0	0		
" 14	140	140	1060	0	0		
" 16	150	450	1040	0	0		
" 17	160	200	1042	+ sl.		+	
" 27	170	60 (?)	1036	+ sl.	+ sl.	0	
" 28	180	320	1040	+ sl.	+ sl.	+ 1% +	
Apr. 3	190	160	1052	+		+ 1%	
" 4	180	60 (?)	1060+	susp. +		+ v'y sl.	
" 5	170	130	1044	0		0	
" 22	120 + .05 gm. post. lobe hypo.	80 (?)	1060	+		+	3%
" 23	100 + .05 gm. post. lobe hypo.	150	1036	+		+	1%
" 24	90 + .05 gm. post. lobe hypo.	60 (?)	1048	+		+	.7%
" 26	80 + .05 gm. post. lobe hypo.	180	1040	0	0	0	
" 30	140	300 (?)	1060	0	0	0	
May 1	180	300	1060+	+		+	
" 4	160	125	1032	0	0	0	0
" 5	170	360	1060	0	0	0	0
" 9	120 + .05 gm. ant. lobe hypo.	40 (?)	1050	0	0	A few bubbles	
" 10	150 + .05 gm. ant. lobe hypo.	250	1020	+	+	+ 1½%	1.2%
" 11	140 + .05 gm. ant. lobe hypo.	80 (?)	1048	+	+	+	.4%
" 12	100 + .05 gm. ant. lobe hypo.	95	1040	0	0	0	0
" 13	120 + .05 gm. ant. lobe hypo.	140	1030	0	0	0	
" 15	140 + .05 gm. ant. lobe hypo.	80	1060	0	0	slight (?)	0
" 16	130 + .1 gm. ant. lobe hypo.	35 (?)	1060	0	0	0	
" 23	170	100	1058	0	0	0	0
" 24	180	360	1040	+	+	+	4%

one year of age, was deprived of a large portion of the pancreas. (The pre-operative tolerance for saccharose by mouth was not established for this individual animal but from our subsequent experiences it can be approximately estimated at 80 to 90 gms.) The animal made a good recovery from the anæsthetic and there were no surgical complications.

December 30.—A spontaneous glycosuria with reduction of Fehling's solution; positive Nylander and fermentation tests and a dextrorotatory substance present. Though the specific gravity remained high there was no demonstrable sugar on the following day.

January 31-March 1.—Assimilation limit for saccharose rose from 60 gms. on February 1 to 90 gms. on February 28, presumably the animal's normal assimilation limit.

March 4. Operation.—Hypophysectomy with removal of posterior lobe and all but a small fragment of anterior lobe. An easy case; no surgical complications.

March 5.—Though the first specimen voided after operation showed glycosuria, 50 gms. of sugar on this date were negative.

March 7-17.—Increasing amounts of sugar failed to give glycosuria until 160 gms. led to a slight reduction—70 gms. over the pre-operative normal.

March 18-April 5.—Further rise in tolerance until 180 gms. gave faint reduction and 170 gms. proved negative.

April 22-26.—Determination of assimilation limit for saccharose, administered with a coincident hypodermic injection of 0.5 gm. posterior lobe extract, showed that glycosuria then occurred with a sugar dosage of between 80 and 90, a lowering of the established tolerance by one-half. In other words, this dose of glandular extract practically restored the pre-operative tolerance.

April 30-May 5.—Demonstration of persistence of the acquired overtolerance at about 180 gms., double the pre-operative normal.

May 9-16.—Determination of assimilation limit with coincident hypodermic administration of .05-0.1 gm. anterior lobe extract showed that this extract is much less potent in reducing the acquired tolerance than is extract of posterior lobe. In other words, 140 gms. of sugar (May 11) was necessary to give glycosuria with .05 gm. of the extract, and double this dose of extract failed to give any reducing properties with 130 gms.

May 23-24.—Demonstration of persistence for two months of acquired tolerance at about 180 gms. (double the pre-operative normal).

July 28.—Four and a half months after the hypophysectomy. Animal has remained in very good condition. Present weight 10.2 kilos—a gain of 2.7 kilos. There had been a particularly rapid gain during the period of sugar feeding, the weight on May 8 having been 11.5 kilos, a gain of 4 kilos or over 50 per cent of the original weight. Animal sacrificed.

Autopsy.—Gross examination showed the only remaining pancreatic tissue to be a small piece attached to the duodenum. There was a persistent and enlarged thymus. The adhesions between the sellar dura and infundibulum made it impossible to estimate in the gross how much of the hypophysis remained. The interpeduncular region, with the remnants of hypophysis and the dura of the sella turcica, was blocked out from the base of the brain after its removal, to be serially sectioned.

Histological.—The tissues removed at operation consisted of the intact posterior lobe and a fairly large fragment of anterior lobe, certifying the surgical procedure. A study of the serial sections of the autopsy material showed a remaining viable fragment of the anterior and of the intermediate lobes.

Comment.—This is the first of the more important observations up to which we are leading. The protocol shows what a high degree of tolerance may be established—practically twice the normal—even in an animal previously deprived of a large portion of the pancreas. It might be supposed that this preliminary operation would in itself have permanently lowered the tolerance, but as a matter of fact it seemed to play no rôle in checking the rapid increase of the assimilation limit after the hypophysectomy. Inasmuch as the supposedly normal tolerance of the animal became restored after the pancreatectomy, it would appear that the remaining fragment of the pancreas had undergone a functional compensation, in so far

as the carbohydrate tolerance may be an index, or else that other members of the ductless gland series had themselves taken part in this compensation.

Following the hypophysectomy the usual transient glycosuria occurred and the animal in the course of the next four months became adipose, gaining about 50 per cent over its former weight. In these respects the effects of the operation were merely comparable to those observed in some of the series of 1908-1909 and recorded by Crowe, Cushing and Homans. However, the increase in weight in this instance was obviously accelerated during the period of sugar feeding. A similar increment in weight has often been observed during such periods of sugar feeding in both man and animals in these states of hypopituitarism.

It was demonstrated for this particular animal, after the final establishment of his high sugar tolerance, that the hypodermic administration of one-twentieth of a gm. of posterior lobe extract given coincidently with the saccharose by mouth, would lower the tolerance practically to its former normal level.[6] On the other hand, it was shown that an equal dose, by weight, of anterior lobe extract similarly administered reduced the tolerance in a slight degree, which, however, was in one way comparable to the reduction shown by the posterior lobe extract.

When it had reached its post-operative level, three weeks after the operation, the acquired high tolerance in this case remained stationary for three months, as shown by the tests on May 1 to 5, and those on May 23 and 24.

D. Effect on the sugar tolerance of removal of the posterior lobe alone.

The foregoing protocols indicate that after a nearly total extirpation of the gland, as well as after the removal of the posterior lobe with varying amounts of the anterior lobe, there occur a primary post-operative fall and a subsequent rise in the tolerance for sugar, whether administered by mouth or intravenously. The results from a single experience suggest, furthermore, that deficiency of the anterior lobe alone plays at least a relatively unimportant rôle in the ultimate acquirement of an assimilation limit exceeding the normal. It remains to report the observations on animals deprived of only the posterior lobe (pars nervosa and its epithelial investment).

Determinations of the sugar tolerance were made upon three animals after operations of this type. In one of them (No. 58) studies were made on the tolerance not only for cane sugar by mouth but also for glucose administered intravenously. In all three of the animals the characteristic post-operative rise in the assimilation limit was demonstrable. This group of cases, therefore, clearly suggests that a determining factor at least in the establishment of the high post-operative tolerance is a deficiency of posterior lobe secretion.

It will be noted that no one of these animals showed the immediate post-operative glycosuria which apparently occurs only when there is considerable traumatism of the stalk. We assume in explanation of this that a simple enucleation of the pars nervosa need not "discharge" the secretion accumulated within this structure.

No. 58.—(Series of 1909-10.) *Determination of tolerance both for saccharose (ingested) and glucose (intravenously) after posterior lobe enucleation. Effect of hypodermic administration of posterior and anterior lobe extracts and of thyroid extract upon the increased post-operative assimilation limit for sugar by mouth.*

TABLE VIII.—TESTS OF TOLERANCE FOR CANE SUGAR FEEDING IN No. 58.

Date.	Grams of cane sugar given.	Granular extract dosage.	Urine.					
			Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
June 12	0	.....	80	1030	0	0		
" 13	70	.....	140	1020	0	0		
" 14	80	.....	80	1030	+	+	+	1.1%
" 15	75	.....	170	1032	0	0		
" 19-24.	Intravenous tolerance of glucose determined (cf. Table IX).							
" 25	Hypophysectomy; enucleation of posterior lobe.							
" 30	70	.....	320	1008	0	0		
July 1	80	.....	220	1012	0	0		
" 2	90	.....	240	1012	+	+	+	.3%
" 3	0	....	160	1040	0	0		
" 7	90	....	120	1050	+	+	+	2.5%
" 14	90	....	180		+	+	d'btful	0
" 18	90	.....	130	1026	+ v'y sl.	+ sl.	0	0
" 20	90	.....	100	1028	+		0	0
" 21	60	.05 gm. post. lobe hypo.	80	1030	+		0	0
" 22	40	.05 gm. post. lobe hypo.	100	1034	0	0	0	0
" 23	50	.05 gm. post. lobe hypo.	50	1042	suspic.	0	0	0
" 25	0	0	120	1042	0	0		
" 29	90	.....	220	1022	suspic.	0	0	0
" 30	100	vomited.						
" 31	50	05 gm. post. lobe hypo.	190	1030	0	0		
Aug. 3	60	.05 gm. post. lobe hypo.	100	1032	suspic.	0	0	
" 4	70	.05 gm. post. lobe hypo.	40	1042	+	+	+	1.2%
" 5	70	.05 gm. ant. lobe hypo.	120	1024	0	0		
" 6	80	.05 gm. ant lobe hypo.	160	1020	0	0		
" 7	70	.1 gm. thyroid hypo.	200	1024	0	0		
" 8	80	.1 gm. thyroid hypo.	90	1036	+	+	+	.6%
" 9	100	0	240	1040	+	+	+	5.2%
" 10	70	.05 gm p. l., .05 gm. a. l. hypo.	40	1042	+	+	+	.6%
" 12	50	Do.	100	1052	0	0		
" 13	60	Do.	50	1050	+	+	+	.6%

Effect also of the intravenous injection of posterior and anterior lobe extract upon the increased intravenous tolerance for glucose. (Tables VIII and IX.)

June 12-24.—A healthy adult, 8 kilo, fox-terrier dog one year of age. Observed for 13 days previous to operation, on the usual diet. *Normal tolerance* to cane sugar by mouth established (June 12-15, Table VIII), at about 80 gms. and for glucose intravenously (June 19-23, Table IX) at 8.75 gms.

June 25. Operation.—A clean-cut enucleation of the posterior lobe, without injury to the anterior lobe or to the stalk. No surgical complications. Dog returned to cage in good condition.

First specimen of urine voided after operation showed no reduction of Fehling's solution.

June 25-29.—A moderate grade of polyuria without glycosuria. (Table IX.)

[6] It is to be noted that animals are apt to lose weight during the administration of posterior lobe extract.

July 7-20.—Post-operative tolerance for saccharose by mouth established at about 90 gms.

July 21.—With 60 gms. of cane sugar (30 gms. below the established tolerance) .05 gm. of posterior lobe extract administered hypodermically gave to the urine a trace of reducing substance. Though this body reduced Fehling's solution it was present in only a very small amount, for it did not cause fermentation with yeast and did not polarize.

July 22-August 3.—Negative tests with .05 gm. posterior lobe extract and coincident feeding of sugar in amounts below 60 gms.

August 4.—Posterior lobe extract (.05 gm. hypodermically) caused a glycosuria with 70 gms. (20 gms. below the tolerance) of cane sugar by mouth.

August 5 and 6.—Anterior lobe extract (.05 gm. hypo.) did not reduce 70 or 80 gms. of sugar.

August 7-8.—Tests with thyroid extract hypodermically showed a slight action in reducing the tolerance. The action of this extract was apparently less potent than was that of the anterior lobe and far less than that of the posterior lobe, twice as large a dose being necessary to produce glycosuria with amounts almost up to the level of tolerance.

August 10, 12, 13.—A combination of anterior and posterior lobe extracts proved only slightly more potent in causing glycosuria than when posterior lobe extract alone was used. Thus .05 gm. of posterior lobe caused a reduction with 60 gms. and was suspicious with 50 (July 23). A combination of .05 gm. posterior lobe and .05 gm. anterior lobe extract gave glycosuria with 60 gms. of sugar, but none with 50. In other words, anterior lobe extract, alone or together with posterior lobe extract, had practically no action in reducing the carbohydrate tolerance for cane sugar taken by mouth.

Comment.—This experience demonstrates that posterior lobe removal alone may cause a post-operative rise in tolerance for ingested saccharose—a rise, to be sure, of little more than 10 gms. in this case and hence not so significant as in the preceding case (No. 35), in which a large part of the pituitary body had been removed. However, it is to be noted that the mere enucleation of the pars nervosa and its immediate epithelial investment necessarily leave much of the pars intermedia unaffected and still capable of discharging "hyaline" by way of the channels of exit for this secretion in the stalk. Hence pars nervosa enucleation means in the average case less of a deficit of posterior lobe (including, of course, pars intermedia) secretion than would be the case with more extensive manipulations, such as characterized the operation in No. 35.

The experience shows, furthermore, that the hypodermic administration of posterior lobe extract is far more efficacious in lowering the post-operative assimilation limit than is an injection of an equal amount of anterior lobe extract. Its powers in this direction are indeed practically equivalent to twice the dosage if made up of equal parts of the extracts of the two glandular subdivisions.

No. 58. (Continued).—*Determination of tolerance for glucose intravenously (simultaneously with that for ingested cane sugar cf. Table VIII) before and after posterior lobe enucleation. Effect also of the coincident intravenous injection of anterior and posterior lobe extract upon the intravenous tolerance to glucose. Post-operative tolerance to lævulose.*

To determine whether in the same animal and under the same conditions the intravenous tolerance for glucose is comparable in its behavior to the tolerance for saccharose by mouth, the following tests were made.

June 20-23.—The *normal tolerance* for glucose given intravenously was established at about 8 gms., approximately one-tenth of that for ingested saccharose.

June 25. Operation.—(Posterior lobe removal.)

June 25-29.—A moderate grade of polyuria without spontaneous glycosuria.

June 28-July 17.—Determination of post-operative intravenous tolerance. This on June 29 was 7.5 gms., slightly below the pre-operative tolerance. On July 13 and 17 it had risen to about 11 gms. or 3 gms. in excess of the pre-operative tolerance.

July 19.—The intravenous injection of 7.5 gms. lævulose caused a marked lævulosuria, equivalent to the glycosuria produced by 11.25 gms. glucose. In others words, the animal was much less tolerant to lævulose than to glucose.

TABLE IX.—TESTS OF TOLERANCE FOR INTRAVENOUS INJECTION OF GLUCOSE IN NO. 58.

Date.	Dosage of extracts injected.	Grams of sugar injected.	Urine.					
			Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
June 20	.....	6.25	180		0	0		
" 21	.....	7.5	200	1034	0	0		
" 22	.....	8.75	170	1032	+	+	+ sl.	0
" 23	.....	0	50	1034	0	0		
	Hypophysectomy (posterior lobe removal).							
" 25	.....	0	1600	1003	0	0		
" 27	.....	0	1180	1008	0	0		
" 28	.....	6.25	150	1030	0	0		
" 29	.....	7.50	70	1032	+	+	+	.3%
July 3	.....	8.75	100	1030	suspic.	suspic.	0	0
" 4	.....	0	160	1040	0	0		
" 5	.....	0	100	1030	0	0		
" 6	.....	10	80	1050	+	+	+	2%
" 11	.....	10	180	1050	0	0		
" 13	.....	11.25	150	1034	+	+	0	.2%
" 17	.....	11.25	100	1040	+	+	+ sl.	.5%
" 19	.....	7.5 gms. levulose	140	1026	+	+	+ sl.	.5% L.
" 26	.05 gm. post. lobe intraven.	6.25	160	1036	0	0		
" 27	.05 gm. post. lobe intraven.	7.50	120	1034	+	+	+	.2%
" 28	.05 gm. ant. lobe intraven.	7.50	120	1042	+	0	0	0
Aug. 14	.05 gm. ant. lobe intraven.	7.50	130	1040	+ sl.	very sl.	0	0
" 15	.05 gm. post. lobe intraven.	7	120	1040	0	0		
" 16			130	1032	0	0		

July 27.—Thirty centimeters of 25 per cent glucose solution, representing 7.5 gms. glucose introduced intravenously, simultaneously with .05 gm. *posterior lobe* extract produced glycosuria—a reduction in tolerance of about 3.5 gms. below the post-operative tolerance and 1.25 gms. below the tolerance determined before operation.

July 28.—An equal amount (7.5 gms.) of glucose intravenously, together with .05 gm. anterior lobe extract produced no glycosuria. Upon a repetition of this dosage on August 14, the urine gave an atypical reduction to Fehling's, but there was no rotation and the fermentation test was negative. Evidently pars anterior extracts were less potent than those trom the pars posterior.

July 29-Aug. 13.—Saccharose ingestion tests (cf. Table VIII).

August 15.—The intravenous injection of 7 gms. glucose with .05 posterior lobe extract caused no glycosuria, establishing the tolerance lowering power of .05 gm. posterior lobe extract intravenously at about 3.5 gms. (cf. July 27), or about 31 per cent of the acquired tolerance of 11 gms.

August 25.—The animal remains in apparently perfect health. Sacrificed. *Autopsy:* Considerable glandular tissue evidently

present in the sella turcica. The interpeduncular block of tissues was preserved and sectioned in the usual manner. Naked eye appearances of the other organs showed nothing noteworthy.

Histological.—The tissue removed at operation showed the intact pars nervosa and its epithelial investment. (Fig. 3.)

Serial sections of the interpeduncular block showed an intact anterior lobe with abundant and hyperplastic pars nervosa about the infundibular stalk. Gland appears collapsed, owing to enucleation of pars nervosa, and replacement of scar tissue in its bed. (Fig. 4.)

Comment.—These further observations on No. 58 illustrate that the post-operative alterations in tolerance for glucose administered intravenously are comparable with those for ingested cane sugar. The early fall and subsequent rise occur in each instance. This continuation of the protocol shows also that the coincident intravenous administration of posterior lobe extract is capable of lowering the acquired post-operative tolerance and that extract of the pars anterior is inactive or far less potent in this respect.

The tolerance for lævulose is shown to be much less than the tolerance for glucose. This, as we shall see, is important in relation to our clinical studies, for we had begun to find at this time that the ingestion of such large amounts of glucose (400 gms.) as were required to obtain the assimilation limit

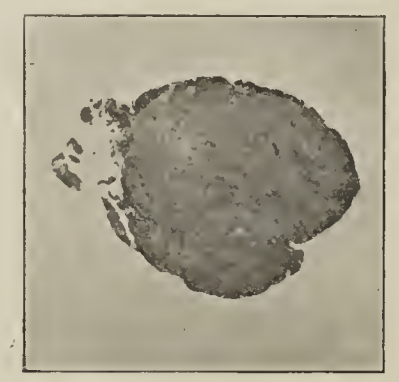

FIG. 3.—No. 58. Sections of tissue removed at operation; intact posterior lobe. Mag. 9 diams. Bensley; 5 μ; iron hæmatoxylin.

in many of our patients could not be retained by the stomach. It is to be noted that after excessive doses of lævulose given intravenously the reducing substance which appeared in the urine was lævo-rotatory. As we shall see, the same holds true for lævulose ingested.

No. 64.—(Series of 1909-10.) *Determination of tolerance for ingested saccharose after posterior lobe enucleation. Increase in tolerance shown as early as 15 days after operation. Ultimate rise to 66 per cent above the normal. Effect of posterior lobe extract (hypodermically, by mouth and intravenously), of anterior lobe extract (hypodermically and intravenously) and of thyroid extract (hypodermically) upon the acquired tolerance.* (Table X.)

May 28-31.—A healthy full-grown, 7.9 kilo, fox-terrier bitch, about one year of age. Observed for five days previous to operation. The *normal tolerance* for ingested saccharose, established at something below 90 gms.

June 1. Operation.—Clean exposure of gland. Pars nervosa readily shelled out from the anterior lobe without bleeding or stalk contusion. Prompt recovery from the anæsthetic.

June 2-3.—Marked polyuria (2250 cc. in first 24 hours) without glycosuria. No post-operative complications. Animal lively and in excellent condition.

June 7-11.—Carbohydrate tests for post-operative tolerance. On June 9, 90 gms. saccharose, the pre-operative assimilation limit, failed to produce glycosuria. On June 11, 110 gms. brought down a reducing body.

June 12-21.—Further increase in tolerance to 140 gms. (50 gms. above the pre-operative normal).

June 22-23.—One-twentieth of a gram of posterior lobe extract administered hypodermically reduced the tolerance of 140 to 110 gms. An equal dosage of anterior lobe extract with 110 gms. gave no glycosuria.

June 24-28.—With 100 gms. of saccharose given each day, and a coincident hypodermic injection of .05 gm. of *posterior lobe* extract on the first day and 0.1 gm. on the second, the animal showed glycosuria on the second day only, indicating that the reduction in tolerance depends upon the dosage of posterior lobe extract. The larger dose (0.1 gm.) of *anterior lobe* extract (for comparison with the above) did not appreciably affect the tolerance, even for amounts of sugar carried up to 120 gms.

June 29.—The administration of 0.2 gm. of posterior lobe extract by mouth, together with 110 gms. saccharose, did not cause

FIG. 4.—Section 41 of 5 μ series from interpeduncular block of No. 58. Mag. 9 diams. Bensley; iron hæmatoxylin. Showing intact pars anterior (P A) with scar (S) at situation of removed pars nervosa; pars intermedia (P I); sellar dura (D); optic chiasm (O G).

glycosuria, showing that administration of the extract by mouth was far less effective than hypodermically.

June 30.—An attempt to compare with the above the effect of an intravenous injection of .05 gm. of posterior lobe extract on the 100 gms. of saccharose ingested caused vomiting of the sugar, but a repetition of the test on *July 19* caused an excessive glycosuria.

July 4-7. The power of thyroid extract given hypodermically in 0.1 gm. dosage was shown to be about equal to that of posterior lobe extracts in lowering the tolerance.

July 19-27.—Attempts to determine the relative dosage necessary, by the different methods of administering the extract, to produce glycosuria with a given amount of saccharose ingested. The extract when administered intravenously was more than twice as potent as when given hypodermically, and by the *latter* method was more than eight times as potent as when taken by mouth.

July 29-August 1.—Observations on the effect of the injection of equal parts of anterior and posterior lobe extracts in 0.1 gm. doses suggested that there might possibly be an antagonistic action; for .05 gm. of posterior lobe extract given alone would have been expected to show glycosuria with the 130 gms. of sugar, in view of the earlier reactions (e. g. June 22), even making allowance for the increment in tolerance between June 23 and August 1.

August 5.—The ultimate tolerance established two months after the operation showed an increase over that determined for June 21. It had risen to about 150 gms., or 60 gms. over the pre-operative normal—an increase in the assimilation limit of 66 per cent.

TABLE X.—TESTS OF TOLERANCE FOR SACCHAROSE INJECTED IN No. 64.

Date.	Grams of cane sugar given.	Glandular extracts used.	Urine. Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
May 28	0	.....	130	1044	0	0		
" 29	80	.....	160	1050	0	0		
" 30	90	.....	120	1032	+	+	+	
" 31	0	.....	180	1030	0	0		
June 1	Hypophysectomy; posterior lobe removed.							
" 2	0	.....	2550	1004	0	0		
" 3	0	.....	500	1010	0	0		
" 7	70	.....	140	1044	0	0		
" 8	80	.....	200	1044	0	0		
" 9	90	.....	160	1030	0	0		
" 10	100	.....	140	1038	0	0		
" 11	110	.....	120	1044	slight	faint	+	1.4%
" 12	0	.....	140	1036	0	0		
" 13	0	.....	80	1040	0	0		
" 14	110	.....	140	1060	0	0		
" 15	120	.....	260	1032	0	0		
" 16	130	.....	160	1036	+ sl.	+ sl.	+	1.3%
" 17	0	.....	140	1034	0	0		
" 18	0	.....	100	1042	0	0		
" 19	130	.....	180	1050	0	0		
" 20	0	.....	200	1038	0	0		
" 21	140	.....	100	1050	+ sl.	+ sl.	+ sl.	.3%
" 22	110	.05 gm. post. lobe hypo.	120	1040	+ sl.	+ sl.	+	.6%
" 23	110	.05 gm. ant. lobe hypo.	250	1028	0	0		
" 24	100	.05 gm. post. lobe hypo.	210	1022	0	0		
" 25	100	.1 gm. post. lobe hypo.	100	1044	+	+	+	.5%
" 26	100	.1 gm. ant. lobe hypo.	180	1032	0	0		
" 27	110	.1 gm. ant. lobe hypo.	270	1018	0	0		
" 28	120	.1 gm. ant. lobe hypo.	320	1020	0	0		
" 29	110	.2 gm. post. lobe by mouth.	540	1020	0	0		
" 30	100	.05 gm. post. lobe intraven.	Sugar regurgitated.					
July 4	100	.1 gm. thyroid ext. hypo.	Sugar regurgitated.					
" 5	100	.1 gm. thyroid ext. hypo.	180	1046	+	+	+	1.4%
" 7	90	.1 gm. thyroid ext. hypo.	120	1026	+	+	+	1.0%
" 19	100	.05 gm. post. lobe intraven.	450	1028	++	+	+	2.6%
" 24	80	.1 gm. post. lobe hypo.	560	1013	0	0		
" 25	90	.1 gm. post. lobe hypo.	380	1028	+	+	+ sl.	.1%
" 26	80	.1 gm. thyroid ext. hypo.	560	1016	+	+	+ sl.	0
" 27	110	.4 gm. post. lobe by mouth.	300	1030	+	+	+	.4% R.
" 28	110	0	420	1012	0	0		
" 29	110	.05 gm. a. l., .05 gm. p. l., intraven.	260	1016	0	0		
" 30	120	.05 gm. a. l., .05 gm. p. l., intraven.	420	1020	0	0		
Aug. 1	130	.05 gm. a. l., .05 gm. p. l., intraven.	260	1024	+	+	+	1.2%
" 2	0	0	120	1018	0	0		
" 3	140	0	140	1030	0	0		
" 5	150	0	160	1034	+	+	+	1.2%

August 15.—Animal apparently in perfect health. Sacrificed. *Autopsy:* conducted in the usual manner.

Histological.—Sections of the fragment removed at operation (Fig. 5), showed pars nervosa with its investment practically intact. Serial sections of the interpeduncular block showed an intact and viable anterior lobe (Fig. 6), with patches of hyperplastic intermediate lobe cells adjoining the stalk and remains of the cleft. The open space from which the posterior lobe was enucleated was apparent.

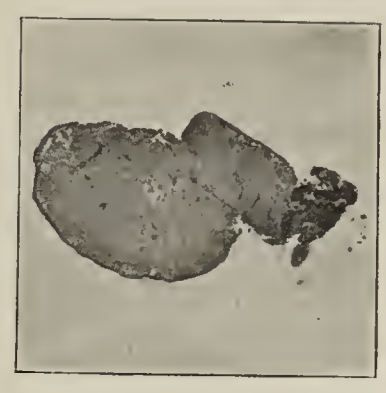

FIG. 5.—No. 64. Section of tissue removed at operation; practically intact posterior lobe. Mag. 9 diams. Bensley; 5 μ; iron hæmatoxylin.

Comment.—This experience likewise demonstrated a gradual increase in the sugar tolerance after posterior lobe removal until it reached 66 per cent above the normal established before the operation. The absence of spontaneous post-operative glycosuria is again to be noted, for there was no stalk traumatism. Tests of the effects of various glandular extracts brought out the following points: that .05 gm. of posterior lobe extract given subcutaneously lowered the acquired

FIG. 6.—Section 22 of 5 μ series from interpeduncular block of No. 64. Mag. 9 diams. Bensley; H and E. Showing space filled with partially organized reticular tissue from which posterior lobe was removed (P L); intact anterior lobe (A L); pars intermedia (P I); enveloping dura (D).

assimilation limit of 140 gms. for ingested saccharose to less than 110 gms., a decrease of 21 per cent; that double this dose of posterior lobe extract brought it down to less than 100 gms., a decrease of about 29 per cent; that equivalent doses of anterior lobe extract given subcutaneously, even with larger doses of sugar, had no comparable tolerance-lowering effect. Thyroid extract, on the other hand, given under the skin likewise, had an equal if not a more potent effect than posterior

lobe extract in this particular animal (not confirmed in No. 67).

Further tests with extracts in this animal showed, as might have been expected, that posterior lobe extract given intravenously is far more effectual than when given under the skin, and that the latter method is in turn far more effectual than when the extract is given by mouth, the relative potency being roughly in the proportion of one to four to thirty-two. This is of some importance in relation to methods of administering the extract for therapeutic purposes.

No. 67.—(Series of 1909-10.) *Determination of the assimilation limit for ingested saccharose after posterior lobe extirpation. Lowered tolerance for nine days; normal tolerance regained on the 12th day; subsequent rapid increase by the third week to 46 per cent above the normal. Tolerance reduced by the administration of posterior lobe extract but not by anterior lobe extract.* (Table XI.)

June 10-14.—The normal assimilation limit for ingested cane sugar in a 7 kilo puppy dog about 10 months of age, was established at something below 75 gms.

June 15. Operation.—A clean-cut posterior lobe removal; the anterior lobe and stalk remaining undisturbed. No complicating factors. The animal stood the procedure well and remained in good condition until sacrificed two months later.

June 15-16.—High grade of polyuria following operation, the first 24-hour amount being 3700 cc. No spontaneous glycosuria in first specimen.

June 18-19.—Glycosuria appeared with 50 gms. saccharose (25 gms. below the normal). Forty grams gave no reducing substance. Tolerance therefore on this third day after operation had fallen 33 per cent.

June 22-23.—Fifty grams no longer gave glycosuria, but it occurred with 60 gms.

June 27-July 7.—Eighty grams were needed to give glycosuria on June 27; 100 gms. on July 1, 110 gms. on July 5, showing the rapid post-operative acquirement of this relatively high assimilation limit. It is presumable that there was a further rise, but no subsequent tests uncomplicated by extracts were made. (The positive reaction with only 100 gms. on August 6th was possibly associated with a prolonged action of the thyroid extract given the day before.)

July 14-August 5.—This interval was consumed in making tests with extracts to determine their relative potency in lowering the raised assimilation limit. The results were somewhat less striking than those shown in No. 64. A coincident subcutaneous injection of .05 gm. posterior lobe extract with 50 gms. saccharose (July 19) gave glycosuria, and again with 40 gms. (July 23)—a lowering of the established assimilation limit therefore by considerably more than half. An equal dose of the extract given intravenously (July 26) gave glycosuria with 30 gms., lowering the established tolerance over 70 per cent.

The injection of anterior lobe extract likewise in .05 gm. dosage had a somewhat less striking effect, but nevertheless gave traces of a reducing substance with amounts of sugar as small as 60 gms. —a lowering of the tolerance about 45 per cent.

The combined action of equal parts of anterior and posterior lobe extracts in .05 gm. doses (July 30-August 3) had if anything less potency than the posterior lobe extract alone.

Double the standard dose of thyroid extract (namely, 0.1 gm.) gave glycosuria with 60 gms. but not with 50 gms. (August 4-5), being, therefore, far less active than posterior lobe extract, in this particular case.

August 8.—The animal remains in apparently perfect health. Sacrificed. *Autopsy:* Conducted as usual, gross examination of the organs disclosing nothing of special note.

Histological.—The tissue removed at operation (Fig. 7) consists of the intact posterior lobe with its epithelial investment, confirming the operative note. Serial sections of the interpeduncular block removed post mortem showed the viable and intact anterior lobe with hyperplastic pars intermedia adjoining the

TABLE XI.—TESTS OF TOLERANCE FOR INGESTED SACCHAROSE IN No. 67.

Date.	Grams of cane sugar given.	Glandular extracts administered.	Urine. Amt.	Sp. Gr.	Fehling.	Nylander.	Fermentation.	Polariscope.
June 10	0		100	1030	0	0		
" 11	80		270	1026	+	+	+	.6%
" 12	70		240	1030	0	0		
" 13	75		220	1020	+	+		
" 14	0		100	1050	0	0		
" 15	Hypophysectomy; removal of posterior lobe.							
" 15	0		3700	1004	0	0		
" 16	0		2150	1004	0	0		
" 17	0		340	1020	0	0		
" 18	50		440	1016	+	+	+	.3%
" 19	40		450	1020	0	0	0	0
" 20	50		470	1020	+ sl.	+ sl.	0	0
" 22	50		310	1020	0	0		
" 23	60		420	1018	+	+	+	.2%
" 24	50		360	1020	0	0		
" 27	80		450	1012	+	+	+	.4%
" 29	80		440	1018	0	0		
" 30	90		500	1008	0	0		
July 1	100		440	1022	susp. +	+ sl.	+	3.1%
" 4	100		80	1052	0	0		
" 5	110		340	1020	+	+	+	.6%
			60	1034	0	0		
" 7	110		340	1022	+	+	+	.3%
" 14	90	.05 gm. post. lobe hypo.	130		+	+	+	2.1%
" 15	70	.05 gm. post. lobe hypo.	80		+	+	slight	1.3%
" 18	60	.05 gm. post. lobe hypo.	150	1055	+	+	+	.5%
" 19	50	.05 gm. post. lobe hypo.	110	1052	+	+	+ sl.	.3%
" 20	70	.05 gm. ant. lobe hypo.	80	1020	+	+	+	.2%
" 21	70	.05 gm. ant. lobe hypo.	180	1020	+	+	+	.5%
" 22	30	.05 gm. post. lobe hypo.	140	1044	0	0	0	0
" 23	40	.05 gm. post. lobe hypo.	70	1054	+	+	+	.5%
" 24	60	.05 gm. ant. lobe hypo.	150	1040	+		0	0
" 25	50	.05 gm. ant. lobe hypo.	150	1042	atypical	0	0	0
" 26	30	.05 gm. post. lobe intraven.	80	1048	+ susp.	+ sl.	+ sl.	.3%
" 27	60	.05 gm. ant. lobe hypo.	120	1030	+	+	+	.3%
" 28	40	.05 gm. ant. lobe hypo.	80	1046	atypical	atypical	0	
" 29	30	.05 gm. ant. lobe hypo.	100	1028	0	0	0	0
" 30	50	.05 gm. a. l., .05 gm. p. l., hypo.	90	1050	+	+	+	.3%
Aug. 1	40	.05 gm. a. l., .05 gm. p. l., hypo.	130	1034	0	0	0	0
" 3	50	.05 gm. a. l., .05 gm. p. l., hypo.	110	1034	+	+	slight	.2%
" 4	50	.1 gm. thyroid hypo.	70	1048	0	0		
" 5	60	.1 gm. thyroid hypo.	60	1052	+	+	+	.6%
" 6	100	0	440	1024	+	+	0	.3%
" 7	90	0	400	1024	0	0		

stalk. Posterior part of the remaining glandular tissue adheres to dural envelope by scar tissue, which has filled the posterior lobe defect.

Comment.—This protocol gives another example of the characteristic temporary lowering of the assimilation limit for ingested cane sugar after posterior lobe removal and the subsequent rapid rise (to 46.6 per cent) in excess of the pre-operative normal limit.

The various tests with glandular extracts, to determine their relative potency in lowering the degree of acquired tolerance, are again recorded. They show that posterior lobe extract is the most efficacious, for in this instance it lowered the acquired high tolerance far below the original normal. Anterior lobe extract was somewhat less effective, thyroid extract still less so. It is quite apparent, however, that in this animal all three extracts showed a greater potency than usual; and to have made the tests of actual value the extracts should have been tried out on the animal's normal tolerance before the operation.

Summary of Experimental Data.

The matter of primary interest to which we would call attention is the increase in the assimilation limit for sugar, whether ingested or given intravenously, in experimentally produced states of hypophyseal deficiency. This acquirement of an over-tolerance for carbohydrates we feel justified in attributing to a

FIG. 7.—No. 67. Section of tissue removed at operation; intact posterior lobe. Mag. 9 diams. Bensley; 5 μ; iron hæmatoxylin.

deprivation of posterior lobe (pars nervosa and pars intermedia) activity.

That operative manipulations of the gland cause a marked disturbance of the sugar storing function is shown by the frequency with which transient spontaneous glycosuria occurs after operations of a certain type—namely, ones which have necessitated a certain degree of traumatism of the infundibular stalk and its enveloping epithelium (pars intermedia). Such operations as do not require stalk manipulation, a clean-cut posterior lobe enucleation for example, usually fail to show this immediate post-operative glycosuria, which therefore can hardly be attributed to the anæsthetic.

Histological studies have shown that the stalk of the hypophysis and the floor of the third ventricle immediately adjacent to it contain, under all circumstances, a substance—Herring's "hyaline bodies"—which may be regarded as the secretory product of the posterior lobe. This material appears to find its way into the infundibular cavity, and the cerebrospinal fluid has been shown to contain a substance having the active properties of posterior lobe extract.[7] The cerebrospinal fluid has an active circulation and in all probability finds its way into the blood stream. It consequently is a natural explanation of the phenomenon of spontaneous glycosuria that in the manipulations of the tissue holding this material an excessive amount of posterior lobe secretion, thus suddenly set free, enters the circulation and thus accounts for the glycosuria. We have found, indeed, that, without injuring or removing the body of the gland, the mere crushing of the stalk by the placement on it of a silver "clip" for the purpose of producing a permanent stasis of the products of posterior lobe secretion, will usually lead to a temporary glycosuria, the procedure being in this respect equivalent to a total removal.

We assume that the spontaneous glycosuria represents a hyperglycæmia from the discharge of stored glycogen which has been set free by the introduction into the circulation (by way of the cerebrospinal fluid) of the posterior lobe secretion

FIG. 8.—Section 37 of 5 μ series from interpeduncular block of No. 67. Mag. 9 diams. Bensley; 5 μ; hæmatoxylin and eosin. Showing pars anterior (P A); hyperplasia of pars intermedia (P I) with colloid cysts; scar tissue (S) replacing posterior lobe cavity; dural envelope (D); optic commissure (O C).

accumulated in the infundibular tissues. We have obtained additional support for this view from some further (unpublished) observations concerning the effects of injections of concentrated cerebrospinal fluids on the carbohydrate assimilation limit of dogs and rabbits.

Preliminary determinations of the tolerance shown by the unoperated animals gave an average assimilation limit for saccharose by mouth of about 10 gms. per kilo of body weight, and for glucose intravenously roughly about one gram per kilo. A marked augmentation—occasionally to double the normal—in the tolerance for sugars administered in either of these ways was an end result of all the hypophysectomies provided the posterior lobe was included with the glandular tissue removed.

[7] Cushing and Goetsch: Concerning the secretion of the infundibular lobe of the pituitary body and its presence in the cerebrospinal fluid. Am. J. Physiol., 1910, XXVII, p. 60.

Though our studies on the influence of various glandular extraets in lowering the assimilation limit in these states of experimentally acquired high toleranee are rather a side issue, nevertheless the faet that posterior lobe extraet proves to be an agent espeeially potent in bringing about a lowered degree of toleranee brings support to the assumption that we are dealing primarily with a defieieney of the posterior lobe.

It may be noted here that attention was ealled in the report by Crowe, Cushing and Homans to the rapid emaeiation whieh follows repeated injections of posterior lobe extraet, due, as they conjeetured, to an aetive tissue oxidation. There was presumably a marked unloading of stored earbohydrates, and glycosuria was oeeasionally observed in their animals. Here, on the other hand, in these states of experimental glandular defieieney, there seems to be a lowered tissue metabolism, manifested by a tendeney to subnormal temperatures and to the aequirement of adiposity. An espeeial rise in the weight curve often oeeurs eoineident with the period of foreed sugar feeding.

Needless to say, in order to have made these observations on the effeet of glandular extraets more conelusive we should have determined their influenee in eaeh case on the normal tolerance as established before the operation.

The attempts to determine the relative efficiency of administering posterior lobe extract by mouth, by subeutaneous injeetion, and intravenously, showed that about one-twentieth of a gram subeutaneously would have a definite effect on the aequired toleranee of the animal. To obtain the same result it required, by a rough estimate, about one-fourth of the dose when given intravenously and eight times the dose when given by mouth. These data are of some therapeutie importanee in relation to the studies on the elinieal cases to follow.[8]

IV. The Sugar Tolerance in Clinical Dyspituitarism.

Our experimental studies had indieated that a defieieney of posterior lobe secretion would lead to an increased toleranee for earbohydrates and that the administration of posterior lobe extract eould markedly lower the acquired high assimilation limit. It was a natural eonjecture that, eould we demonstrate the existenee of similar reactions toward the earbohydrates in the elinieal eases of pituitary disease whieh were under our eare, we might possibly have a means of determining whether there was a state of over or under glandular activity, at least so far as the posterior lobe was eoncerned.

Methods of estimating the tolerance.—We have unfortunately received but little help from earlier studies, for though it has been roughly estimated that the normal human assimilation for glueose by mouth is about 150 gms., and for lævulose about 100 gms., we have found no figures as to the average sugar toleranee for man in relation to body weight. In the eanine, as will be reealled, eertain approximate standards for the normal were found—namely, about 10 gms. of ingested eane sugar per kilo of body weight and about one gram per kilo for glueose administered intravenously. These proportions, of course, were not expected to hold true for man; and if they did, sueh enormous doses of sugar would be required as to make their administration out of the question. As it was, we experienced diffieulties, even though carbohydrates are appetizing to these individuals almost without exeeption.

We began our observations with the simple administration of glueose usually given on an empty stomaeh about five hours after the evening meal, all subsequent specimens of urine being separately saved. In many of the eases the tolerance for glueose was so great that we were never able to determine the aetual assimilation limit, vomiting the sugar taking plaee in spite of all preeautions and devices sueh as disguising the taste, giving divided doses and the like. We have had individuals take and retain 400 gms., as the following records of sugar feeding will show, but this is exceptional, and when the assimilation limit was very high we were usually foreed to desist from our efforts to determine it by ingestion methods.

A personal experienee has shown us that the stomach may rebel even at the relatively small doses required to determine the assimilation limit for presumably normal states, and it takes gastrie eourage for patients to consume two or three times this amount.

We have done better with lævulose, and it is our impressiou, from one or two experienees with individuals (Cases XIII and XVI), whose stomaehs tolerated the sugars well, that only about half the bulk needed with glueose is required to reaeh the assimilation limit with lævulose. It is of interest that, as in the animal experiments, the exeess of lævulose absorbed from the intestine appears uneonverted as lævulose in the urine. It may be reealled that Strauss[9] regards the oecurrence of lævulosuria after the ingestion of amounts below 100 gms. as an evidenee of hepatic insuffieieney. The assimilation of three times this amount in some of our eases would seem to indieate an extraordinary storage eapaeity for glyeogen.

A rough estimate might plaee the average human assimilation limit for ingested glucose in a 70 kilo individual at something over 140 gms. of glueose, or about two grams per kilo of body weight, only a fifth of the eanine toleranee; and for lævulose at about 100 gms. or 1.4 gms. per kilo. Though the majority of our cases of hypopituitarism with high grades of sugar toleranee had beeome adipose, nevertheless the eomparative inerease in the tolerance limit per body weight was extreme, in many running up to three and even four or five gms. of glucose per kilo.

One interesting result of the eonsecutive earbohydrate tests to which we have subjeeted these generously eo-operating patients has been the rapid inerease in weight eoineident with the sugar administration. A similar effeet was noted with the canine feedings. It is to be remembered, at the same time, that the observed individuals, experimental or elinieal, usually

[8] We desire to express our obligations to Mr. F. M. Bell of Armour & Company for his generous co-operation in supplying us with the powdered preparations of posterior lobe which have been used in these experiments.

[9] H. Strauss: Zur Funktionsprüfung der Leber. *Deutsche med. Wchnschr.*, 1901, XXVII, p. 757.

show a subnormal temperature, and it is a natural suggestion that the oxidizing powers are at a low ebb and that the stored glycogen is transformed into fat. In the brief abstracts which we have given of the experiments we could not go with any detail into the histological studies of the other ductless glands, though it may be said in passing that the general features of the changes throughout the whole body consist in a striking deposition of fat within the cells.

The experimental subcutaneous administration of posterior lobe extract in repeated doses appears to bring about the reverse picture—namely, excessive emaciation—and, as we have seen, small individual doses serve to lower either the normal sugar toleranee or the high tolerance succeeding posterior lobe removal. This suggests, of course, a ready means of determining the tolerance for ingested sugars in clinical cases. Thus, coincident with the administration by mouth of an amount of sugar which would represent the presumed normal tolerance according to the body weight, the dosage of the extract necessary to produce a transient glycosuria can be determined (cf. Case XIII). This, however, requires further investigation and better methods of administration, for the subcutaneous or intermuseular injection even of one-twentieth of a gram of the boiled extract suspended in 2 cc. of fluid is apt to produee an uncomfortable point of tenderness, and in one patient caused a local amicrobic abscess.

Tolerance in Acromegaly and Gigantism.—It has been known for a number of years that a spontaneous glyeosuria is a not uncommon accompaniment of acromegaly, a malady in whieh hypophyseal overactivity has been assumed by many. Indeed, attention has been called to the fact that a lowered assimilation limit may be associated with pituitary lesions in the absence of any clinical manifestations of acromegaly. An interesting illustration of this had been given in one of our own cases observed before we began these experimental studies on sugar tolerance. The patient, who exhibited certain obscure cerebral symptoms thought to be of vascular origin, was regarded at first as the subject of diabetes mellitus, and subsequently, as the glycosuria disappeared and marked polyuria persisted, as a case of diabetes insipidus. At autopsy a year or two later a gumma of the anterior lobe was disclosed. Our present interpretation of the case would be that the lesion had stimulated the pars nervosa into an abnormal activity.

Other examples of spontaneous glyeosuria which we are inclined to attribute to a pituitary body lesion rather than to the upsetting of a eerebral "sugar-center" might be given. We are inclined to the view that the fleeting glycosurias whieh aecompany certain bursting fractures of the cranial base are of this nature, for the line of fracture usually seeks out the middle cranial fossa and may readily traumatize the pituitary body itself.

However, in none of the twenty cases of acromegaly or gigantism which have occurred in our personal series, has there been a coincident spontaneous glycosuria. The reason for this doubtless lies in the fact that the cases have been seen late in the progress of the disease. In all probability had the urine been examined at a suffieiently early stage, glycosuria, or at least a lowered tolerance, might have been detected. In one instance, indeed, the patient had failed to pass a life insurance examination some years before, as he was supposed to be suffering from diabetes, though at the time of his admission to our care an abnormally high assimilation limit was present.

It is presumable that the syndromes of acromegaly and gigantism primarily represent states of hypophyseal, and as we believe of anterior lobe overactivity, it being a natural eonjecture that the posterior lobe meanwhile is functionally stimulated. As the disease progresses and the pituitary struma forms (whether it be a simple hyperplasia, a cyst or "malignant adenoma") a condition of glandular insufficiency results and states comparable to those seen in the animals with experimentally defective glands are superimposed. In other words, there appears to be, at least for such outspoken states of hyperpituitarism as we have up to this time come to recognize clinically (represented by aeromegaly and gigantism), an inevitable tendency for them to be transformed ultimately into states of hypopituitarism.

The case reports will be given in the greatest brevity, for all that we wish to show is the high degree of carbohydrate tolerance aequired by these patients. In a few instanees sufficient doses of posterior lobe extract have been given to produce glycosuria with amounts of sugar below the established assimilation limit.

We have subdivided the acromegalies into separate groups according to the duration of the symptoms. In only one of these patients (Case I) was the condition reeent and acute, possibly of not more than a year's duration. A subnormal tolerance was present, namely 1.4 gms. of glueose per kilo of body weight.

CASE I.—No. 25827. *April 25, 1910.* (Acromegaly.)—Male, aged 33, weight 72 kilos (160 lbs.). Urine, high specific gravity; no sugar.

May 1.—Glucose 100 gms. Glycosuria on first three specimens.

May 5, 6, 7.—Glucose in 25, 50 and 75 gm. doses respectively gave no reducing body.

May 8.—Glucose 100 gms. gave glycosuria on first specimen.

In the following case the symptoms were of about four years' duration and were not particularly outspoken. The patient was not fat. The tolerance was about normal, approximately 150 gms. or 2 gms. of glucose per kilo of body weight.

CASE II.—No. 27247. *January 10, 1911.* (Acromegaly.) Male, aged 40, weight 73 kilos (162 lbs.).

January 15 and 17.—Glucose 100 gms. gave an atypical, and 150 gms. a strong reduction to Fehling's.

January 22 and 23.—Lævulose 100 gms. gave an atypical, and 150 gms. a strong reduction to Fehling's.

January 25.—Lævulose 100 gms. with 0.4 gm. post. lobe ext. gave a strong reduction.

The disease in the two suceeeding patients, both females, was of about five and eight years' duration respectively, judging from the onset of the amenorrhœa. They were tested only with lævulose, for which they showed a fairly high tolerance, 1.7 gm. per kilo in the first and 2.4 gms. per kilo in the second case. There were no posterior lobe injections.

Case III.—No. 27256. January *23, 1911.* (Acromegaly.) Female, aged 37, weight 84 kilos (188 lbs.).

January 24.—Lævulose 100 gms. gave an atypical reduction.

January 25.—Lævulose 150 gms. gave a positive reduction in a single specimen nine hours after ingestion.

Case IV.—No. 27290. *February 1, 1911.* (Acromegaly.) Female, aged 35, weight 66 kilos (148 lbs.).

February 4.—Lævulose 150 gms. gave an atypical reduction in first two specimens.

February 5.—Lævulose 175 gms. gave a positive glycosuria in first two voidings seven and nine hours later.

The three following cases were of longer duration. The first had progressed rapidly during a period of about four years and showed pronounced neighborhood symptoms due to a "malignant adenoma" of the pars intermedia (?). The assimilation limit for ingested glucose was never fully determined, but it was over 5 gms. per kilo of body weight.

The second was a slowly progressive case of 13 years' duration, with a small gland and no neighborhood pressure symptoms. The sugar tolerance for glucose was 3 gms. per kilo of body weight.

The third was a case of about six years' duration, associated with an intrathoracic goitre. This had caused disturbing pressure symptoms, and the patient in the past few months had lost the 50 pounds in excess of his previous normal weight which he had put on since the onset of the disease. His tolerance for glucose could not be established, but it was enormous and possibly over 5 gms. per kilo of body weight.

Case V.—No. 25971. *May 1, 1910.* (Acromegaly.) Female, aged 28, weight 64 kilos (142 lbs.).

May 6.—Glucose 300 gms. in divided doses gave an atypical reduction.

May 14.—Glucose 250 gms. with 0.1 gm. post. lobe ext. subcutaneously gave a positive reduction (1.5 per cent dext. rotatory).

May 16.—Lævulose 100 gms. gave no reduction.

May 19, 22 and 24.—Glucose in 100, 200 and 300 gm. doses respectively gave no glycosuria. Larger doses were not retained.

Case VI.—No. 26210. *July 6, 1910.* (Acromegaly.) Male, aged 40, weight 85 kilos (191 lbs.).

July 6 and 7.—Glucose 100 gms. and 200 gms. respectively was negative.

July 8.—Glucose 300 gms. heavy reduction.

July 9.—Glucose 250 gms. slight reduction with first voided specimen.

Case VII.—No. 25977. *May 21, 1910.* (Acromegaly.) Male, aged 59, weight 70 kilos (156 lbs.).

July 2.—Glucose 200 gms. 10 a. m., and 200 more 10 p. m., gave no reduction.

July 4.—Glucose 300 gms. in one dose gave no reduction.

July 6 and 7.—Glucose in 400 gm. amounts vomited on each trial.

The three following cases belong in the group of acromegalic giants or actual gigantism. The increase in height was not marked in the first patient who in many respects was a typical example of acromegaly, beginning in about the 22d year of life. There were no neighborhood symptoms. The second patient was a huge acromegalic giant with an enormous gland, causing blindness; and the third was a typical giant, with a huge sella turcica, the symptoms dating from childhood. These individuals were naturally very heavy, but nevertheless the tolerance in terms of body weight was above normal. In the first case it was 2.2 gms. per kilo; in the second and third it could not be established, but was shown to be something over 2.6 gms. per kilo.

Case VIII.—No. 26068. *June 8, 1910.* (Acromegaly.) Male, aged 42, weight 90 kilos (200 lbs.).

June 9, 10 and 11.—Glucose in 100 gm., 150 gm. and 175 gm. doses respectively gave no glycosuria.

June 13.—Glucose 200 gms. gave a positive reduction of 0.4 per cent by the polariscope.

Case IX.—No. 27045. *December 10, 1910.* (Acromegalic giant.) Male, aged 35, weight 116 kilos (257 lbs.), height 197 cm. (6 ft. 6 in.)

December 12.—Glucose 200 gms. negative.

December 14.—Glucose 200 gms. with 0.2 gm. ant. lobe ext. subcutaneously, negative.

December 15.—Glucose 300 gms. with 0.4 gm. ant. lobe ext. subcutaneously, negative.

December 16, et seq. Patient unable to retain amounts over 300 gms. Tolerance not established. Lævulose not tried. An increase of five pounds in weight during the 5 days of sugar feeding.

Case X.—No. 25947. *May 15, 1910.* (Gigantism.) Male, aged 36, weight 134 kilos (276 lbs.), height estimated at 7 ft. 6 in.

May 20, 23, 28 and 30.—Glucose 100 gms., 200 gms., 275 gms., and 300 gms. respectively gave no glycosuria. Subsequent trials with amounts over 300 gms. were vomited. Actual assimilation limit for glucose not reached. Lævulose not tried.

June 12.—Glucose 175 gms. with 0.1 gm. post. lobe ext. subcutaneously gave no reduction.

June 13.—Glucose 250 gms. with 0.1 gm. post. lobe ext. subcutaneously gave no reduction.

Further tests omitted owing to discomfort from the injections.

These 10 examples, therefore, of outspoken acromegaly or gigantism, representing conditions which we attribute to primary anterior lobe hyperplasias, have shown gradations in tolerance varying from something below 100 gms. of ingested glucose to amounts possibly far in excess of 400 gms. Had we been fortunate enough to have observed a patient in the very early stage to which, presumably, spontaneous glycosuria is largely confined, the series, from the standpoint of sugar tolerance, would have been complete. Assuming as we do at present that the disturbed limits for sugar assimilation are associated in large part, if not solely, with posterior lobe lesions, it is conceivable that the malady might run its course without seriously disturbing the carbohydrate tolerance—in other words, without inciting the primary increase and subsequent decline of posterior lobe activity.

Step by step with the acquired increase of sugar tolerance shown by these patients, other symptoms which we attribute to deficiency of glandular activity become more or less prominent—general weakness and drowsiness, a subnormal temperature, a low blood pressure, amenorrhœa or impotence, and, above all, the adiposity already commented upon. The acquired power of storing carbohydrates is, in other words, merely one of many clinical manifestations of glandular (posterior lobe) insufficiency, but it furnishes a clinical test by means of which it is possible to estimate in a measure the stage at which the malady has arrived, and it may therefore

come to serve as a therapeutic index of the required glandular dosage.

Tolerance in States of Primary Hypopituitarism.—Of more interest than the foregoing group of cases are those in which there has been from the outset a deficiency of posterior lobe activity. They are of greater moment also, for they have been widely overlooked. In their most striking form these various conditions of hypopituitarism are brought about (1) by direct pressure upon the infundibular stalk by interpeduncular tumors, often having a congenital anlage; (2) by direct involvement of the posterior lobe in a growth originating in the gland itself, or (3) by the distant effect of a tumor causing an obstructive hydrocephalus and thus damming back the fluid medium carrying the posterior lobe secretion.[10]

As the following data abstracted from our case histories will show, we have had numerous opportunities for testing the sugar tolerance of patients afflicted with the lesions comprised in the first two of these three subdivisions. The same symptoms of hypopituitarism that we have recounted above as occurring late in acromegaly, under these circumstances appear as the primary manifestations of the malady—adiposity being one of the most striking features. The presence of an interpeduncular or pituitary tumor in many of these 11 cases to be recorded was certified by operation or autopsy or else by the existence of definite neighborhood symptoms which, aided by the X-ray rendered the diagnosis beyond dispute.

Only one of these patients showed a subnormal assimilation limit. This was a mixed case in which a large infundibular tumor was associated with suggestive acromegalic changes in the bones of the hands, marked adiposity (the weight being 213 lbs.), and a low tolerance for ingested glucose, on a single test 100 gms. giving a positive glycosuria. The condition was one for which no adequate explanation offered itself, except on the basis of an overactive anterior lobe combined with an underactive posterior lobe. At autopsy a year later the gland, though intact, was found to be somewhat compressed by the growth, which had greatly elongated the stalk and had doubtless obstructed the posterior lobe secretion.

The typical cases of primary hypophyseal tumor showing no trace of acromegaly which have occurred in our series and which have had their sugar tolerance estimated are as follows. In the first two cases the tolerance for ingested glucose alone was determined. Both were patients with pronounced neighborhood symptoms. The assimilation limit of 400 gms. in the second case was particularly high, in view of the body weight, namely 5.7 gms. per kilo.

[10] These matters have been fully discussed by one of us in a detailed description, as yet unpublished, of the clinical aspects of these states (Cushing: Clinical aspects of dyspituitarism. Lecture before the Harvey Society, New York, December, 1910).

It has been found by Cushing and Jacobson that the cerebrospinal fluid, particularly in cases of obstructive hydrocephalus, has the same power in reducing the assimilation limit of the dog and rabbit that is possessed by the extract of the posterior lobe itself, another indication, in addition to these recorded by Cushing and Goetsch, that the cerebrospinal fluid is the medium which carries the products of posterior lobe secretion.

CASE XI.—No. 25806. *April 20, 1910.* (Hypophyseal "adenoma.") Male, aged 36, weight 88 kilos (195 lbs.).

April 26.—Glucose 100 gms. negative.

April 27.—Glucose 200 gms. positive; 1.2 per cent dext. rotatory.

April 29.—Glucose 100 gms. with 0.1 gm. post. lobe ext. gave glycosuria.

May 1. Operation.—Partial tumor extirpation. Subsequent increase in weight.

May 23, June 4, June 5, June 7, June 8.—Glucose in doses of 100 gms., 150 gms., 175 gms., 200 gms. and 225 gms. respectively gave no glycosuria. Larger doses were not retained by the stomach, so that the *ultimate tolerance* was only roughly estimated at something over 2.6 gms. glucose per kilo of body weight.

CASE XII.—No. 26634. *September 26, 1910.* (Hypophyseal tumor.) Male, aged 32, weight 70 kilos (157 lbs.).

September 29, 30 and October 1.—Glucose in 200, 300 and 400 gm. amounts retained. No glycosuria.

October 6.—0.1 gm. post. lobe injection without sugar feeding gave no glycosuria.

October 7.—0.2 gm. post. lobe injection without sugar feeding gave no glycosuria.

October 11. Operation.—Sellar decompression. No post-operative glycosuria. No further feedings.

In the following case sugar was well taken and it was possible to make comparative tests of the tolerance for ingested glucose and lævulose, it being shown that the assimilation limit for glucose was by weight of sugar about twice that for lævulose. The tolerance for glucose was 4.9 gms. per kilo of body weight; for lævulose it was 2.3 gms. per kilo. A gain of 5 lbs. in weight occurred during the sugar feeding. The case is important also in that it was the first of our series in which a definite therapeutic dosage for ingested extract was established on the basis of giving enough gland to produce a transient lævulosuria, with an amount of lævulose which would have represented the assimilation limit of a normal individual of an equal body weight. This was about 30 gms. below her estimated limit.

CASE XIII.—No. 27619. *April 12, 1911.* (Hypophyseal "adenoma.") Female, aged 30, weight 71 kilos (158 lbs.).

April 13.—Lævulose 150 gms. gave a suggestive reduction.

April 14 and 15.—Glucose in 200 and 250 gm. doses was negative.

April 16.—Glucose 300 gms. gave a suspicious reduction.

April 18.—Glucose 350 gms. positive. *Estimated limit* 325.

April 19.—Lævulose 160 gms. positive. *Estimated limit* 150.

April 20. Operation.—Removal of a large portion of the tumor (or hyperplastic gland) by the usual infralabial approach. Good recovery.

May 3.—Treatment with whole gland feeding instituted in 0.2 gm. doses three times a day. Marked subjective improvement. No spontaneous glycosuria.

To determine a more accurate basis for the glandular therapy the following tests were made with increasing amounts of glandular extract ingested while the sugar amounts remained stationary.

May 10.—Lævulose 120 gms. with 0.6 gm. of whole gland extract divided in three doses during the day. No reducing substance in urine.

May 11.—Lævulose 120 gms. with 1.2 gm. divided in three doses during the day. Positive reduction in specimen on evening of this day. Positive Seliwanoff test for lævulose. Estimated therapeutic dosage, therefore, 0.4 gm. of the whole gland extract three times a day.

Judging from the estimates given by the preceding record on the lævulose basis alone, the three following cases show an

enormous increase in the assimilation limit for sugars—in *Case XIV* 200 gms., or 2.8 gms. per kilo; in *Case XV* 300 gms., or 4.3 gms. per kilo, and in *Case XVI* also 4.3 gms. per kilo. If we are to multiply these figures for weight of ingested lævulose by two, the amount of glucose necessary to reach the limit of tolerance would in many cases easily exceed the individual's capacity of its retention.

Case XIV.—No. 27419. *March 13, 1911.* (Hypophyseal "adenoma.") Female, aged 34, weight 72 kilos (160 lbs.).

March 14.—Lævulose 150 gms., atypical reduction.

March 15.—Lævulose 200 gms., a slight but definite reduction. *Estimated limit.*

Case XV.—No. 27156. *January 1, 1911.* (Infundibular tumor.) Female, aged 40, weight 69 kilos (154 lbs.).

January 3 and 4.—Lævulose 100 gms. and 200 gms., both negative.

January 5.—Lævulose 300 gms. gave a slight reduction on the third specimen. *Established limit.*

Case XVI.—No. 26250. *July 16, 1910.* (Hypophyseal tumor.) Male, aged 27, weight 69.7 kilos (155 lbs.).

July 18, 19, 20, 22.—Glucose in increasing doses of 150, 200, 250 and 300 gms. caused no glycosuria. An increase in weight of 1.6 kilos (3.5 lbs.) occurred during these feedings.

July 24.—Glucose 350 gms. vomited.

July 26.—Glucose 200 gms. with 0.1 gm. post. lobe ext. gave glycosuria with 0.4 per cent dext. rotation.

August 3. Operation.—Sellar decompression.

August 23.—Glucose 200 gms. negative.

August 25.—Glucose 300 gms. positive, a post-operative lowering of the limit, presumably from liberation of post. lobe from pressure. *Tolerance* for ingested glucose estimated at 4.3 gms. per kilo.

April 20, 1911.—Returned for observation, with an advance in adiposity, etc.

April 24, 26, 28.—Lævulose in 150, 160 and 200 gm. doses gave no reduction.

April 29.—Lævulose 250 gms. gave a slight reduction in the first specimen.

May 5.—Lævulose 250 gms. gave an atypical reduction.

May 6.—Lævulose 300 gms. gave a *positive lævulosuria* by Seliwanoff's test. (Compare Case XXI.)

There remain in this series of patients subjected to the sugar tests several in whom the symptoms of glandular insufficiency were equally outspoken, though the neighborhood pressure disturbances were relatively insignificant. Alterations in the sella turcica, however, were present in many of them. Thus in Cases XVI and XVII, the latter a typical instance of Fröhlich's syndrome, the glandular fossa was exceedingly small. That a condition of glandular insufficiency need not depend upon the presence of a tumor needs no comment. Indeed in all probability a primary glandular hypoplasia is just as common a starting point for hypopituitarism as it is for hypothyroidism and the clinical states arising from disturbances of one or the other of these glands are in all probability equally frequent.

In the following case, as in Case XIII, sugar was well borne so that comparative estimates for lævulose and glucose could be roughly established at 4.7 gms. of glucose per kilo. and 2.9 gms. of lævulose per kilo.

Case XVI.—No. 27140. *December 29, 1910.* (Sexual infantilism with painful adiposity.) Female, aged 23, weight 59 kilos (132 lbs.)

December 30.—Glucose 200 gms. negative.

January 1, 1911.—Glucose 300 gms., slight reduction. *Estimated limit* 280.

July 12.—Lævulose 150 gms. negative.

July 13.—Lævulose 200 gms. positive. *Estimated limit* 175.

The next case was a typical example of infantilism of the *typus Fröhlich.* The assimilation limit for lævulose was 150 gms., or 2.8 gms. per kilo.

Case XVII.—No. 27421. *November 13, 1910.* ("Dystrophia adiposo genitalis.") Male, aged 9, weight 54 kilos (120 lbs.).

November 12.—Lævulose 100 gms., negative.

November 15.—Lævulose 150 gms., positive on first specimen. *Established limit.*

The two succeeding cases are similar ones, with adiposity and amenorrhœa. The first patient showed definite neighborhood symptoms and was epileptic. Her tolerance for glucose was about 200 gms., 3.3 gms. per kilo. The second patient assimilated glucose up to 275 gms., 2.7 gms. per kilo.

Case XVIII.—No. 25715. *April 4, 1910.* (Hypophyseal adiposity with infantilism.) Female, aged 14, weight 61 kilos (136 lbs.).

April 6, 11, and May 6.—Glucose in 50, 100 and 150 gm. amounts was negative.

May 9.—Glucose 200 gms. positive, 0.4 per cent dext. rotation. *Established limit.*

May 14.—Glucose 100 gms. with 0.1 gm. post. lobe ext., negative.

May 17.—Glucose 150 gms. with 0.1 gm. post. lobe ext., negative.

May 23.—Glucose 175 gms. negative.

May 28.—Glucose 175 gms. with 0.1 gm. post. lobe ext. positive, 0.6 per cent dext. rotation.

Case XIX.—No. 25694. *March 31, 1910.* (Hypophyseal adiposity.) Female, aged 15, weight 103 kilos (230 lbs.).

April 8, 15, 20, 29.—Glucose in amounts of 50, 100, 150 and 200 gms. was negative.

June 4, 5.—Glucose 225 gms. and 250 gms. respectively, negative.

June 6.—Glucose 275 gms. not retained.

June 7.—Glucose 275 gms. retained and gave glycosuria, 0.6 per cent. dext. rotation. *Established limit.*

June 10.—Glucose 200 gms. with 0.1 gm. post. lobe ext., negative.

Both of the following patients would have been regarded as typical instances of "adiposis dolorosa" with amenorrhœa, and their association with a pituitary lesion might have been overlooked had it not been for the fact that both showed definite symptoms—an early hemianopsia in one case and an enlarged sella, with pituitary headaches, in the other. Both showed a high tolerance, which, however, is less striking in relation to the body weight, owing to the extreme adiposity. In the first case the tolerance for glucose at 400 gms. represented a little over 3 gms. per kilo.

Case XX.—Surgical No. 26679. *October 4, 1910.* ("Adiposis dolorosa" with neighborhood symptoms.) Female, aged 55, weight 123 kilos (273 lbs.).

October 25. Operation.—Sellar decompression.

November 1.—Hypophyseal therapy (9 grains daily of the whole gland extract) caused polyuria.

November 12.—Glucose 300 gms. negative.

November 14.—Glucose 400 gms., faint reduction. *Limit.*

The tolerance in the following case when first observed was about 275 gms., or 3.4 gms. per kilo. On readmission six months later there had been an increase in weight and a marked advance in the assimilation limit for glucose beyond the patient's capability to retain it. Her assimilation limit for lævulose had come to exceed the former limit for glucose by weight of sugar, namely, about 320 gms., or 3.6 gms. per kilo of existing body weight. (Compare Case XVI.)

CASE XXI.—No. 26225. *July 10, 1910.* (Hypophyseal adiposity.) Female, aged 24. Weight 81 kilos (181 lbs.).

July 10.—Glucose 150 gms. negative.

July 11.—Glucose 250 gms. atypical reduction.

July 13.—Glucose 300 gms. not retained.

July 14.—Glucose 300 gms. retained. Urine showed heavy reduction (not polarized). *Estimated limit* 275.

January 11, 1911. Readmission.—Gain in weight of 6.7 kilo. Glucose not retained in early tests.

January 22 and 23.—Lævulose 10 and 200 gms. negative.

January 24.—Lævulose 300 gms. gave an atypical reduction after 9 hours. *Estimated limit* 320.

January 28.—Lævulose 200 gms. with 0.4 gm. post. lobe ext. gave a positive reduction with Fehling's.

Summary of Clinical Data.—These bare records of the carbohydrate tolerance as it has been observed in the clinical cases of dyspituitarism suffice to show a striking parallelism with the protocols which we have given of the experimentally induced states of hypophyseal insufficiency. Their similarity is at all events enough to justify the assumption that here too we are dealing with a condition of altered activity of the posterior lobe.

Under both circumstances, apparently regardless of the influence of the pars anterior, the acquirement of a high carbohydrate assimilation limit goes hand in hand with other features which we are inclined to attribute to posterior lobe insufficiency and which appear to indicate a lowering of metabolic activity—notably a subnormal temperature, a dry skin, a low blood pressure, a large appetite (especially for carbohydrates), and marked deposition of fat throughout the body.

In these conditions then of primary or secondary involvement of the hypophysis, interfering with the normal production of glandular secretion and producing, among other things, a marked rise of the carbohydrate tolerance, glandular therapy should be instituted, perhaps taking the tolerance as an index for the amount of glandular extract to be given.

We are merely on the threshold of these carbohydrate studies in clinical cases, and fully recognize that the observations have been crudely made. They will necessitate quantitative determinations and better methods both of sugar administration and of giving the extracts. The latter problem is particularly important, if we are to advance the therapy of these conditions at least to the point where thyroid therapy now stands.[11]

[11] In this connection the observation in Case XIII is particularly worthy of note, as giving some lead as to the dosage essential to the individual case on the basis of the carbohydrate tolerance. The patient weighed 71 kilos and showed an overtolerance for lævulose, the limit being estimated at 150 gms. Judging that her normal tolerance for lævulose would have been about 120 gms. she was given sugar in this amount on consecutive days. Meanwhile the amount of extract was increased until a positive transient melliturıa followed the sugar administration. This established the amount of extract at 0.4 gm. (6 grains) three times a day as the therapeutic dose. It is to be noted that we are here speaking of "whole gland" feeding with the realization that it is the posterior lobe extract which the preparation contains that is the essential element. Though we have worked with isolated posterior lobe preparations in the experiments in the laboratory, they are as yet too expensive for prolonged administration such as these individuals need.

V. CARBOHYDRATE TOLERANCE IN RELATION TO DUCTLESS GLANDS IN GENERAL AND TO THE HYPOPHYSIS IN PARTICULAR.

Glycosuria in its relation to lesions of the central nervous system received abundant attention after the first impulse given to the subject by Claude Bernard's discovery. The exact location, however, of his so-called sugar center seems never to have been precisely determined, and we have experimental evidence that glycosuria may likewise be produced by a *piqure* or other injury of the brain stem anterior to the medulla.

On the clinical side it was noted by several of the earlier writers that glycosuria was not infrequent in cases of basal brain tumor. Curiously enough, however, this proved to be more true of growths situated in the interpeduncular neighborhood than of those involving the hind-brain. Indeed Loeb [12] pointed out that it was actually a more frequent manifestation of tumors in the region of the hypophysis than of those supposedly in the neighborhood of Bernard's "center"; and more recently Stern and Josefson, to quote from Messedaglia,[13] have shown that clinical melliturıa has been the exception (3 cases only) in the 36 reported cases of cysticercus of the fourth ventricle.

In explanation of the occurrence of diabetes with certain hypophyseal tumors Rath [14] in 1888 offered the suggestion that alterations might have taken place in the composition of the cerebrospinal fluid which caused it to act as an irritant upon the nervous structures—an interesting assumption, in view of our recent demonstration that the posterior lobe actually discharges its secretion into the cerebrospinal fluid. Others as Pineles [15] and Strümpel [16] explained the condition as

[12] M. Loeb. Hypophysis Cerebri and Diabetes Mellitus. *Centralbl. f. innere Med.*, 1898, XIX, p. 893.

[13] Messedaglia. Lesioni dell' ipofisi e glicosuria. (Reprint.) Reviste Sintetiche, Milan, No. 30, 1903.

[14] Rath: Ein Beitrag zur Kasuistik der Hypophysistumoren. Inaug. Diss. Göttingen, 1888.

[15] Pineles. Ueber die Beziehung der Akromegalie zum Diabetes Mellitus. *Jahrb. d. Weiner k. k. Krankenanst.*, 1895, IV, Part II, p. 27.

[16] Strümpel. Ein Beitrag zur Pathologie und pathologischen Anatomie der Akromegalie. *Deutsche Ztschr. f. Nervenheilk.*, 1897, XI, p. 51. In his interesting detailed report of a case Strümpel makes the following deduction: "Den Hypophysistumor als Ursache der Glycosurie anzunehmen, ist unmöglich, da Hypophsistumoren auch ohne Glykosurie vorkommen." A similar deduction has misled others into the statement that because tumors of the hypophysis are found without acromegaly therefore this malady cannot be attributed to the tumors which have been found present in certain cases.

possible only on the basis of a concomitant pancreatic lesion, and still others hypothecated the existence of centers, other than that of Bernard's, which presided over the glycogenic function. Such centers were postulated for the pons, for the optic thalamus, the cerebellar and cerebral peduncles, and finally Loeb offered the interesting suggestion, which was supported by Caselli and accepted by a number of subsequent writers, that the *tuber cinereum* (the cortical tissue around and including the infundibulum) might be a sugar center.

In more recent years a furtherance of our knowledge of these glycosurias of supposedly encephalic origin has come about indirectly through the many investigations upon the rôle played in carbohydrate assimilation by the functional activity of the various glands of internal secretion.[17]

The relationship of the pancreatic islets to the more common and more persistent forms of clinical diabetes was clearly shown by the important studies of Opie and others, but only of late has the attention which they deserve been given to other ductless glands in so far as their activities influence carbohydrate metabolism. It has become evident that all of the glands, either by their primary action or through interrelation with other members of the series, play a part in sugar metabolism. It is known, for example, that experimentally induced thyroid insufficiency leads to an increased tolerance for sugars,[18] while the studies of Eppinger, Falta and Rudinger[19] have indicated that removal of the parathyroid bodies has a contrary effect, namely, a lowering of the carbohydrate assimilation limit. Furthermore, experimental hyperglycæmia and glycosuria have been produced by injections of epinephrin, which apparently exercises its influence through the splanchnic control of the glycogenic function of the liver.[20]

Clinical corroboration of these laboratory findings have been many. Thus the carbohydrate tolerance in hypothyroidism (myxœdema) has been found in many clinical cases to be high and, contrariwise, in hyperthyroidism—a condition which as yet has not been experimentally reproduced—it is known that the assimilation limit is below the normal. Indeed, in extreme grades of exophthalmic goitre spontaneous glycosuria may occur, and it has been observed that the administration of thyroid extract in adequate dosage may precipitate an actual glycosuria in the patients with exophthalmic goitre in whom it does not spontaneously occur.[21]

However, one need not turn to actual morbid states to find striking illustrations of perverted tolerance for carbohydrates. A particularly good example occurs in pregnancy, with its remarkable alterations in metabolic activity—alterations which are unquestionably an expression of change in the activity of all of the glands of internal secretion and not of the ovary and its contained corpus luteum alone. The accompanying thyroid hyperplasia is well known, but an even more striking change, taking place in the hypophysis cerebri, has been brought to light by Erdheim and Stümme's important study.[22] We have been able to substantiate their disclosure that the hypophysis is not only much enlarged during pregnancy but that the *pars anterior* shows a characteristic and unmistakable histological picture.

Clinical observers have long known that as a result of repeated pregnancies evidences of hypophyseal hyperplasia may occur, even to the point of producing such neighborhood symptoms as a transient bitemporal hemianopsia. Furthermore, in this state the carbohydrate metabolism becomes altered in ways which are similar in many respects to the changes which we have recounted. Thus in a series of pregnant women observed by Reichenstein,[23] it appeared that out of 93 cases 11.8 per cent showed actual mellituria, while in others a decreased carbohydrate assimilation limit, especially for lævulose, was demonstrated. Indeed, a transient spontaneous lævulosuria occurred in some of the cases after parturition.

Doubtless comparable alterations in sugar tolerance occur in other periods of physiological readjustment. It is not unlikely that the glycosurias of adolescence may prove to be coupled in some way with deviations in the internal secretions which are on the borderline of the physiological normal. In view of the occurrence at this period of life of a rapid increment particularly in skeletal growth, it is a natural conjecture that these glycosurias may be related as closely to an hypophyseal hyperplasia as to the more obvious changes of the interstitial cells of testis and ovary which occur at this time. But the facts already established make a sufficiently connected story to justify the avoidance of speculation.

We have already referred to the frequent coincidence of mellituria with acromegaly. Hanseman in 1897 collected reports of 97 cases, 17 of them having shown glycosuria, and he expressed the opinion that the percentage of positive findings would have been much larger had the cases been sufficiently observed. Strümpel, in the same year, suggested that future investigations of the sugar tolerance in this malady would demonstrate for all cases a lowered assimilation limit even though spontaneous glycosuria might be absent. It apparently was his view that some underlying factor affecting metabolism brought about both of these conditions rather than that one of them was dependent in any way upon the

[17] It is to be noted that, if our view as to the method of secretory discharge from the posterior lobe into the cerebrospinal fluid is supported by the investigations of others, this part of the gland will be removed from the ductless gland series in so far as they are grouped together on the basis of their products of secretion being taken up directly by the blood stream.

[18] McCurdy. The influence of thyroidectomy on alimentary glycosuria. *J. Exper. Med.*, 1909, XI, p. 798.

[19] Eppinger, Falta and Rudinger. Ueber die Wechselwirkung der Drüsen mit innerer Sekretion. *II Mitteil., Ztschr. f. klin. Med.*, LXVII, p. 380.

[20] Underhill and Clossen. *Am. J. Physiol.*, 1907, XVII, p. 42.

[21] Kraus and Ludwig: Klinische Beiträge zur alimentären Glycosuria. *Wiener klin. Wchnschr.*, 1891, IV, No. 46, p. 855 and No. 48, p. 897.

[22] Erdheim and Stümme: Ueber die Schwangerschaftsveränderung der Hypophyse. Beiträge z. path. Anat. u. z. all. Path., 1909, XLVI.

[23] Reichenstein. Glykosurie und Schwangerschaft. *Wiener klin. Wchnschr.*, 1909, XXII, p. 1445.

other. Hinsdale, in 1898, found that glycosuria had been noted in 14 out of 130 reported cases of acromegaly, and subsequently Launois and Roy [24] recorded 16 cases with "diabetes" the post-mortem finding in three instances having shown a pituitary enlargement.

The evident suggestion from these clinical observations, that the hypophyseal lesion played at least a certain rôle in eliciting the glycosuria, naturally led to certain experimental attempts to reproduce the condition. These attempts were necessarily limited to destructive glandular lesions; and that the end results of the partial extirpations by Rogowitsch, Caselli, and Friedman and Mass were negative in this respect is now readily explained by the analysis of the protocols which we have given. The experiments, in other words, were productive of an ultimate increase (unfortunately unobserved) rather than the expected persistent lowering of the sugar assimilation limit.

The recent clinical and experimental studies of Borchardt [25] have been far more suggestive than any heretofore made. In an investigation of 176 recorded cases of acromegaly he found that spontaneous glycosuria had occurred in 63 and that in eight others there was a lowered assimilation limit—all told, therefore, 71 showed a deficient carbohydrate metabolism. On the other hand, none of the cases of hypophyseal tumor unassociated with acromegaly which had been reported since 1886 showed glycosuria. The query was naturally raised as to why such a discrepancy should exist if the stimulation of a supposed sugar center in the *tuber cinereum* were actually the cause of the glycogenolysis in the former cases.

Borchardt was able to find in the literature only 10 cases of acromegaly without spontaneous glycosuria, in which the tolerance for ingested sugars ("alimentary glycosuria") had been tested. Of these, all but two were positive, that is, they showed an assimilation limit below the normal. He comments, however, on the fact that there may be considerable variation from time to time in the individual's tolerance, and gives one specific instance of an acromegalic who had shown spontaneous glycosuria five years previously and yet at the time of his observation gave a negative reaction to 150 gms. of glucose. Had Borchardt looked upon this as the rule rather than the exception for the later stages of the disease, he would doubtless have anticipated the main outcome of our own studies.

Acting on the assumption, therefore, that there was a persistently lowered carbohydrate tolerance in the disease and that it was occasioned by an overactivity of the gland, he endeavored to simulate this condition, not by glandular extirpation, but by the hypodermic administration of an extract derived from the whole gland. He was able to show, especially in rabbits, that this extract caused hyperglycæmia and glycosuria, the reducing body being glucose. With dogs his results were much less convincing, the only satisfactory result being obtained in a partially pancreatectomized animal soon after the operation. Later, however, in this same animal no glycosuria could be obtained. (Compare our Protocol No. 35.) Though appreciating the insufficiency of his experimental proofs, Borchardt interpreted his results as at least suggestive of the fact that hypophyseal hyperactivity was responsible in the clinical cases for the glycosuria. He made no distinction, it will be noted, between the anterior and posterior lobe and the possible individual rôles played by these subdivisions of the gland.[26]

This brief sketch of some of the more important earlier studies suffices to show that glycosuria is known to be a frequent accompaniment of acromegaly associated with a hypophyseal tumor or hyperplasia, and on the other hand, as pointed out by Borchardt, that tumors of the hypophyseal neighborhood unassociated with acromegaly do not cause this symptom, which therefore can hardly be attributed to the stimulation of a neighboring sugar center. Furthermore, experimental removal of the gland has failed to cause a permanent lowering of the tolerance, indeed, Borchardt's observations in the reverse direction, simulating hyperfunction of the gland by the injection of the glandular extracts, have shown that under these circumstances there is at least a temporary tolerance lowering effect.

As the outcome of our laboratory and hospital studies we believe that not only these few established facts concerning the relation of the hypophysis to sugar tolerance but also some of the conjectural views, those of Rath and of Loeb for example, as well as many of the apparent discrepancies which have been the outgrowth of attempts to refute them, are easily correlated and readily explainable on a single basis. This is that conditions of overactivity or functional hyperplasia of the posterior lobe (*pars nervosa et intermedia*) foster glycogenolysis and occasion a lowered sugar tolerance if not an actual glycosuria, whereas in conditions of lowered

[24] Launois and Roy. Glycosurie et Hypophyse. *Compt. rend. Soc. de biol.*, 1903, LV.

[25] Borchardt. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie. *Ztschr. f. klin. Med.*, 1908, LXVI, p. 332.

[26] Some doubt has been raised concerning Borchardt's results by the subsequent studies of Franchini (Die Function der Hypophysie und die Wirkungen der Injection ihres Extraktes bei Tieren. *Berlin. klin. Wchnschr.*, 1910, No. 14-16), who was unable, except with massive doses either subcutaneously or intravenously to produce glycosuria either in rabbits or dogs. Franchini is inclined to attribute the positive results obtained by Rossi (Il Tommasi, 1909, No. 25-26) in support of Borchart's findings to the fact that Rossi used carbolic acid as a preservative of his extracts, a substance which of itself may cause glycosuria. Our own results with the injection of posterior lobe extract and concentrated cerebrospinal fluids confirm Borchardt's findings in so far as they show that a spontaneous glycosuria in normal rabbits is easily elicited, and we have found that a definite lowering of the assimilation limit occurs in normal dogs.

These discrepancies are possibly attributable to the various methods of preparing the extracts. Our own extract is supplied from the dried and powdered posterior lobe. This, according to weight of powder, is dissolved in the desired number of centimeters of boiling water. This sterilizes the powder and does not affect the active principle, which is not only very soluble but very resistant to heat. The supernatant fluid is used for the injection. For the feeding tests the powder itself is used.

activity or hypoplasia the carbohydrate tolerance becomes distinctly higher than the normal.

Thus it is our belief that the *experimental observations* in the past have been for the most part regarded as negative through misinterpretations, three important factors having been overlooked: (1) that *it is the posterior lobe secretion which is chiefly concerned in these deviations from the normal in the tolerance for carbohydrates;* (2) that *a persistent lowering of the assimilation limit can be brought about only by an overactivation of this part of the gland* and the physiological state is one which as yet cannot be experimentally reproduced. Finally (3) that *glandular extirpations which include the posterior lobe lead to a terminal increase in sugar tolerance rather than to the long sought for lowering of the assimilation limit.* So far, therefore, as the simulation of conditions of disease is concerned, experimental investigations of the function of this or of any other of the ductless glands is narrowed largely to the negative method of study through extirpation, for we know of no way of stimulating any one of these structures into a condition of persistent overactivity, the injection of extracts by no means answering the purpose.

The past *clinical observations* on the relation of hypophyseal disease to sugar tolerance have been similarly misconstrued, as the following essential factors have been overlooked: (1) that *the posterior lobe secretion is here again primarily concerned;* (2) that *in acromegaly, whether or not there exists, as there often does, an obvious tumor or hyperplasia of the pars anterior, there is in the early stages a coincident primary posterior lobe hyperplasia which is responsible for the glycosuria, or lowered assimilation limit; and* (3) that *inasmuch as the posterior lobe secretes into the cerebrospinal fluid rather than directly into the blood stream, a condition, comparable to a posterior lobe hypoplasia, is produced not only by all interpeduncular tumors which actually compress the gland but also by all distant ones which obstruct the cerebrospinal fluid outflow; and finally a functional hypoplasia occurs as the end-result of the actual pituitary struma which characterizes acromegaly.* All of these stages are productive of posterior lobe insufficiency and lead to an over-tolerance for carbohydrates.

There is still much difference of opinion in regard to the ætiology of acromegaly, and even in the minds of those who are inclined to attribute the disease to an hypophyseal lesion —implying usually the pars anterior—there are doubts as to whether it is the outcome of a lessened or an increased glandular activity. It is our own view that at least the skeletal changes of the malady are an expression of an anterior lobe hyperplasia, which occasionally becomes transformed into an extensive tumor formation (the adenomas and sarcomas of many writers). However this may be, in the early stages of the disease there is seemingly an activation of the posterior lobe leading, among other symptoms, to the glycosuria or lowered tolerance which we have discussed: in the later stages, through actual destruction, or invasion, or compression of the posterior lobe and pars intermedia, a state of posterior lobe insufficiency supervenes, with an increase of carbohydrate tolerance.

This same effect upon posterior lobe secretion, and consequently upon sugar tolerance, is brought about in similar fashion by a primary hypoplasia of the posterior lobe or by a superimposed (interpeduncular) tumor, or, thirdly, by a remote lesion which has produced an internal hydrocephalus. Unfortunately in the past, studies of carbohydrate assimilation have been directed almost solely toward the investigation of states of lowered sugar tolerance, to the utter neglect of the more common states of greatly increased tolerance which not only seem to be inevitable in advanced cases of acromegaly but which constitute the main metabolic disturbance in the variously named cerebral, or what we should prefer to call hypophyseal, adiposities—dystrophia adiposo-genitalis, adiposis dolorosa, and many of the hydrocephalies—as well as in some of the diverse states of feminism and infantilism which are encountered.

We think that our experiments have afforded the first satisfactory interpretation of the conflicting results of preceding studies, showing, as they appear to do, in the first place, that a discharge of posterior lobe secretion caused by manipulation of the infundibular stalk is responsible for the spontaneous temporary glycosuria, which appears, as noted by Caselli and others, soon after the operation; in the second place, that a deficiency of posterior lobe secretion, as simulated by partial or total removal of this lobe in dogs, occasions an increased tolerance to carbohydrates; and thirdly, that administration of posterior lobe extract by mouth, hypodermically or intravenously has the power of diminishing this acquired overtolerance.

The precise manner of action of the posterior lobe secretion in producing hyperglycæmia and glycosuria—whether by a direct glycogenolytic effect, or by some influence exerted on the sympathetic antonomic nervous system as seems to be the case with adrenalin, or in other ways—must remain unanswered for the present. It has been conjectured that the extract might have an action similar to phlorizin and cause a renal lesion, allowing the normal sugar content of the blood to pass through the kidneys; but this seems unlikely in view of the fact that we have been able to show for the dog what Borchardt demonstrated for rabbits, namely, that the administration of hypophyseal extract produces a hyperglycæmia. Others have advanced the idea that some effect of the extract on the pancreas would prove to be the underlying factor in the glycosuria; and this it will be recalled was the view of Pineles and Strümpel. We have confirmed the statement of Sweet and Pemberton that posterior lobe extract acts in a fashion similar to adrenalin in inhibiting the external flow of pancreatic juice, and it is conceivable that it may likewise exert an influence on the internal secretion of the islets, but this hardly seems to be the direction which the final explanation of these phenomena will take.

On the clinical side, we believe that the data which we have given will have a considerable therapeutic significance, for on the basis of existent carbohydrate tolerance it should be possible to determine whether a particular case of obvious hypophyseal disease is associated with an over or under activity of the posterior lobe, and thus whether it is advisable or not to ad-

minister glandular extract. Our clinical series make it apparent that in the early stages of acromegaly the sugar tolerance is apt to be low but that later in the disease there is an acquired overtolerance; furthermore, that a high assimilation limit may be expected from the outset when the gland is compressed or obstructed by a superimposed tumor which brings about alterations comparable to those of a primary posterior lobe hypoplasia. Hence it may be assumed that in the early stages of acromegaly glandular therapy is contraindicated, whereas later in the disease its use would seem to be highly advisable. The circumstances are similar to those relating to the administration of thyroid extract, which is contraindicated in Basedow's disease but gives such brilliant results in myxœdema. It is clear, furthermore, that hypophyseal extract is indicated in all of the cases of hypopituitarism which are brought about by obstructive agencies (tumors or hydrocephalus). Our best clinical results of glandular therapy have been seen in cases of this type, and the dosage, we believe, should be estimated for each case on the basis of the individual's grade of tolerance for carbohydrates.

VI. SUMMARY.

I. *Experimental Studies.*—We have shown that the secretory product of the posterior lobe (*pars nervosa et intermedia*) is discharged into the cavity of the third ventricle and becomes dissolved in the cerebrospinal fluid, a medium which passes from the ventricles to the subarachnoid spaces and thence, in all probability, enters the blood stream by way of the dural sinuses.

Under various forms of operative manipulation of the infundibulum and hypophyseal stalk—structures which appear to hold the reserve deposit of posterior lobe secretion—a transient hyperglycæmia is produced, presumably due to the setting free of an excess of this secretion, which in turn causes the discharge of stored glycogen. For the succeeding few days the assimilation limit for ingested carbohydrates is considerably diminished. "alimentary glycosuria" being produced by a smaller amount of sugar than was previously required.

If the operation has been so conducted as to create a subsequent and permanent insufficiency of posterior lobe secretion (either owing to the removal of a considerable portion of this lobe with its epithelial investment, or through interference with its secretory discharge either by the placement of a "clip" on the stalk, or by so damaging it that an infundibular cicatrix forms) the temporary lowering of the assimilation limit is succeeded by an abnormal and enduring augmentation in the tolerance for sugars.

The assimilation limit for carbohydrates, greatly increased under these circumstances, can be promptly lowered by the coincident intravenous or subcutaneous injection of posterior lobe extract. This extract, furthermore, has a pronounced effect in lowering the sugar tolerance of the normal animal in whom it may even cause glycosuria when given in sufficient dosage.

Certain associated symptoms are apt to accompany the increased tolerance for carbohydrates. One of these is a tendency toward the acquirement of a generalized adiposity, which suggests the conversion of the stored sugars into fat. Thus, during the tests to establish the carbohydrate tolerance, whether in experimental or clinical cases of posterior lobe deficiency, there often occurs a notable accretion in body weight. The individuals are apt to have a subnormal body temperature, suggesting an imperfect oxidizing or metabolizing capacity, and this persistently lowered temperature can be raised by the injection of glandular extracts. Conversely, repeated hypodermic injections of posterior lobe extract in the normal animal are apt to cause a profound degree of emaciation, presumably from excessive tissue katabolism; and a lowered carbohydrate tolerance is demonstrable during such an administration of the extract.

For these reasons we believe, contrary to the opinion advanced in a previous paper by Crowe, Cushing and Homans, that the tendency toward adiposity displayed by partially hypophysectomized animals is not due solely to a deficiency of anterior lobe secretion.

II. *Clinical Studies.*—In view of the fact that the products of posterior lobe secretion enter the cerebrospinal fluid, it is apparent that any intracranial lesion occasioning stasis of this fluid will lead to symptoms of posterior lobe insufficiency. An internal hydrocephalus therefore, of whatever origin, is doubtless the most common source of moderate grades of this condition. Tumors which arise in the interpeduncular space and directly compress and deform the infundibular attachment and thus "block" the secretion furnish another not infrequent source of the same symptoms. A third form of posterior lobe deficiency occurs as a late manifestation of a pre-existing hypophyseal hyperplasia—much as, in the case of the thyroid gland, evidences of myxœdema in the course of time, are likely to supervene on states of hyperthyroidism.

It is well known that hyperglycæmia is of frequent occurrence in acromegaly and gigantism—clinical states which presumably represent, at the outset at least, a condition of hyperpituitarism, the pars anterior doubtless being chiefly responsible for the skeletal changes. We believe, however, that there is an inevitable tendency in these states toward an ultimate glandular insufficiency—toward dyspituitarism, in other words. Hence, in all probability a lowered sugar tolerance will be found only during the active stages of these maladies. Thus in all but two of the ten cases of acromegaly that we have studied, the individuals have begun to show present evidences of posterior lobe hypoplasia which are recognizable through the laboratory experiences with animals suffering from comparable states which have been experimentally produced. They are acquiring adiposity, have subnormal temperatures, and often show an extraordinarily high carbohydrate assimilation limit. In view of this marked transition from a low to a high sugar tolerance which occurs during the progress of the malady, the discordant results of the past studies of metabolism in acromegaly are not surprising.

As polyuria is apt to be associated with these pituitary

lesions, whether experimentally produced or the outcome of disease, a clinical picture readily mistaken for diabetes mellitus or diabetes insipidus may be present. It is not improbable, furthermore, that the fleeting glycosurias following fractures of the base of the skull are induced by trauma of the posterior lobe or its infundibular attachment—glycosurias, in other words, which are comparable to those which can be elicited by operative manipulation of these structures.

In view of the ease with which a transient hyperglycæmia may be produced by these hypophyseal lesions, it is possible that our views in regard to the glycosurias, at least those of supposed encephalic origin, need some revision.

If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the secretion of the hypophyseal posterior lobe greatly enhances their power in this respect. In view of the generalized adiposity, not confined to the panniculus alone, but observable also in liver and muscle as well as in the other organs in these states, it would seem that functional deficiency of the posterior lobe permits the excess of stored carbohydrates to be transformed into fat.

In these states of beginning adiposity indicating a pituitary hypoplasia, glandular administration is indicated, and it is possible that the therapeutic dosage for the individual case may be determinable on the basis of the quantity of extract necessary to produce melituria with an amount of ingested sugar which would be expected to represent the individual's normal assimilation limit.

DISTORTIONS OF THE VISUAL FIELDS IN CASES OF BRAIN TUMOR.[1]

STATISTICAL STUDIES. (FIRST PAPER.)

By Harvey Cushing, M. D., and George J. Heuer, M. D.,
The Johns Hopkins Hospital, Baltimore, Md.

INTRODUCTORY.

Of the manifold symptoms which may be produced by an intracranial growth none are of greater interest and none of greater importance than the various disturbances on the part of the visual apparatus. On the one hand, largely irrespective of the seat of the lesion the direct ophthalmoscopic examination of the eye-grounds may reveal the characteristic neuroretinal stasis and œdema (choked disc), which unfortunately is still regarded by many as essential to the diagnosis of tumor, despite the fact that it is a comparatively late pressure phenomenon. On the other hand, deviations from the normal outlines of the visual fields not only may serve as the only possible means of determining the situation of the growth, but may at times even foretell the onset of a choked disc, for certain distortions of the color field boundaries appear to be brought about by general pressure disturbances.

Hence the ophthalmoscope, though chiefly useful in disclosing the most reliable of the objective signs of increased intracranial tension, nevertheless is of some value for localization, as it may show upon which side the tension is greater. The perimeter, contrariwise, is chiefly useful as an aid to localization, though it furnishes at the same time important information in regard to the existence of an increase of tension. These two instruments, therefore, are the most useful and should be the most used of all the paraphernalia accessory to the making of a neurological investigation; and, needless to say, every physician and every surgeon who desires to make an intelligent study particularly of intracranial tumors must familiarize himself with these important diagnostic aids, without which he would be as helpless as the clinician unfamiliar with the stethoscope in the presence of a cardiac lesion.

As the outcome of some investigations relating to the subject of choked disc, started by one of us in 1905 in conjunction with Dr. James Bordley, it has become our clinical routine not only to make frequent, often daily, observations on the condition of the eye-grounds, but also to make serial tests of visual acuity and repeated perimetric charts of form and color before and after our operative procedures. Dr. Bordley drew attention early in the course of these studies to the frequent association of color interlacing with low grades of increased intracranial tension. In a communication dealing primarily with this subject[2] comment was also made upon certain matters which bear relation to the subject of hemianopsia. The more important of them in the present connection, was the fact that in cases of homonymous hemianopsia the color inversion or interlacing is demonstrable for the seeing half of the retina just as it is for the entire field when there is no regional implication of the visual pathway.

Since presenting this earlier paper in May, 1909, correspondingly detailed studies have been made of 104 additional cases of tumor, and we desire in the present communication to record the results of perimetry in the entire series of 200 surgically treated cases which have been observed during the past five years.[3]

One must be familiar from personal experience with the

[1] This communication is the first of a series of five papers, the four to follow dealing respectively with dyschromatopsia and with the binasal, bitemporal and homonymous hemianopsias which have been observed in a series of 200 cases of brain tumor.

[2] Bordley and Cushing: Alterations in the color fields in cases of brain tumor. *Arch. Ophth.*, 1909, XXXVIII, p. 451.

[3] The fields in these cases have been plotted by Drs. Bordley, Heuer, Crowe, Goetsch and Sharpe, and when there has been any question of inaccuracy on the part of patient or observer, or any unusual peculiarity of the fields, they have been replotted by a second observer who has not seen the original charts, in order to eliminate the possible errors of personal equation.

tedium incidental to the careful plotting of the visual fields to fully realize the amount of patience and time often required if a reliable record is to be secured. The individual performance is fatiguing enough, alike to observed and observer, but when alterations are taking place from day to day, so that serial performances are called for, one could hardly subject himself and his patient to the ordeal were not the results often of vital importance, either in presaging the necessity of prompt relief from pressure or in estimating the quality of relief which the operation has afforded. Naturally, in many of our surgically fatal cases but a single perimetric examination has been made before the operation, but in far the larger number a series of charts has been plotted—as many as ten or twenty in some instances where patients have been kept long under observation after simple palliative measures. While awaiting the time for a "silent" lesion to finally give evidence of its location, the condition of the visual fields—the color relationship in particular—taken in conjunction with the degree of œdema of the nerve-head, is the most accurate means of estimating the need of further intervention.

The color inversion and choked disc of the average tumor in its early stage disappear as a rule after the usual subtemporal decompression. One must, however, in these cases have the expectation that the relief will be only temporary and that further intervention will be necessitated after a number of months, even though no localizing signs have as yet appeared. Hence, an examination of these patients every few weeks or months is advisable in order that a return of the pressure symptoms may be promptly recognized. Thus it is that in many of our cases the fields have been plotted a great number of times; and in the series of authenticated tumor cases there are, all told, some four hundred perimetric charts appended to the histories, and if the charts of the patients under the suspicion of carrying a tumor were added to these the number would doubtless be doubled.

How helpless one may actually be in attempting to make a regional diagnosis without the aid of perimetry is realized most effectually in the case of young children or of blind patients whose fields have not been previously taken. When a choked disc has advanced to the stage of complete atrophy the occipital lobes and optic radiations become "silent," so far as any objective signs useful for a regional diagnosis are concerned, and in several of our patients the localization of lesions which proved post mortem to have been accessible and removable has been completely frustrated in this way.

A number of the patients who were blind upon admission have brought fields which had been plotted elsewhere before the total loss of vision occurred. Though these records have occasionally been useful, they have, as a rule, been so casually taken—in one case, indeed, the blind areas were actually reversed on the cards—that most of them (even those plotted by skilled ophthalmologists, have been too unreliable for diagnostic purposes. Too few circumferential points are usually taken and the cards, as a rule, are so small that the color interlacing, on which we have come to lay so much stress, is not apparent. Furthermore, a number of our best illustrations of hemiachromatopsia were entirely overlooked on tests made shortly before the patients' admission to the hospital, the fields for form alone having been recorded.

How accurate one needs to be in plotting the charts is well illustrated by a recent experience in which an erroneous observation of our own was fortunately corrected for us by Dr. Adolph Meyer, whose description of the course taken by the geniculo-calcarine fibers is of primary importance.[4] The story is as follows:

SURGICAL NO. *26762*.—The patient had been shot in the left eye five years before admission. The missile had destroyed the eyeball, necessitating enucleation, and had produced an immediate, total and permanent left facial paralysis with complete deafness in the left ear. He recovered from the effects of the injury, but after some months began having peculiar seizures with inaugural subjective disturbances of taste and smell. These attacks gradually became more severe and in the course of time led to typical convulsive fits with a gustatory aura, smacking of the lips and a final loss of consciousness—typical uncinate gyrus fits.

On examination there was a total peripheral palsy of the left seventh and eighth nerves, and with the X-ray a bullet was shown lodged in the petrous portion of the left temporal bone. There was a scar nicking the lower left eyelid, and it was apparant that the missile in its course must have transversed the lower part of the temporal lobe.

In view of Dr. Meyer's description of the temporal loop of the optic radiation it seemed probable that the perimeter would show a partial right hemianopsia, or at least some defect in the field of the remaining (right) eye. The fields were consequently taken (Fig. 1), and were interpreted as being normal. Fortunately Dr. Meyer saw the patient at this time and suggested that the fields be replotted, with a closer angulation, namely, for every fifteen degrees at least. When this was done the defective sector which he had foretold was disclosed in the upper outer quadrant (Fig. 2), corresponding with the damaged fibers of the lower part of the pathway in the injured temporal lobe. The defect, of course, would have been a bilaterally homonymous one had the left eye not been destroyed.

This experience serves as a good illustration of the care essential to the making of these records. A further need for precaution which is not fully appreciated lies in the possibility of misjudging the existence of a tendency to vertical hemianopsia. For in these cases it is necessary, in order to accurately determine the superior and inferior points on the vertical meridian, that the disc be advanced toward the fixation point only a few degrees from the median line, first on one side and then on the other. If the median line alone is relied upon and the disc happens to be advanced toward the center merely a degree or two from the exact mid-line and on the side of the blind field, the highest (or lowest, as the case may be) median point will be missed and the field boundary will appear to slant across instead of dropping away rather abruptly from the poles of the vertical meridian. Unless regard is paid to this, an existing tendency toward hemianopsia may be entirely overlooked. This applies to the color fields as well as to that for form, and in estimating the field for form (or for white) in suspicious cases gray discs are

[4] Adolph Meyer: The connections of the occipital lobes and the present status of the cerebral visual affections. *Trans. Ass. Am. Physicians*, 1907.

often useful, for the form outline may seem intact with the usual white disc and yet vision in one or the other half fields be definitely obscured.

There are other precautions which are more familiar and to which attention is more often called—the avoidance of distortions from fatigue and inattention, the distinction of the white from the form fields, the employment of pure and uniform colors, and the like.[5]

Statistical Review.

All told, in the period of twenty-one years, from January 1, 1890, to January 1, 1911, 242 patients with cerebral neoplasm have been operated upon in Professor Halsted's clinic at the Johns Hopkins Hospital. In the first fifteen years of this period, from January 1, 1890, to June 18, 1904, only

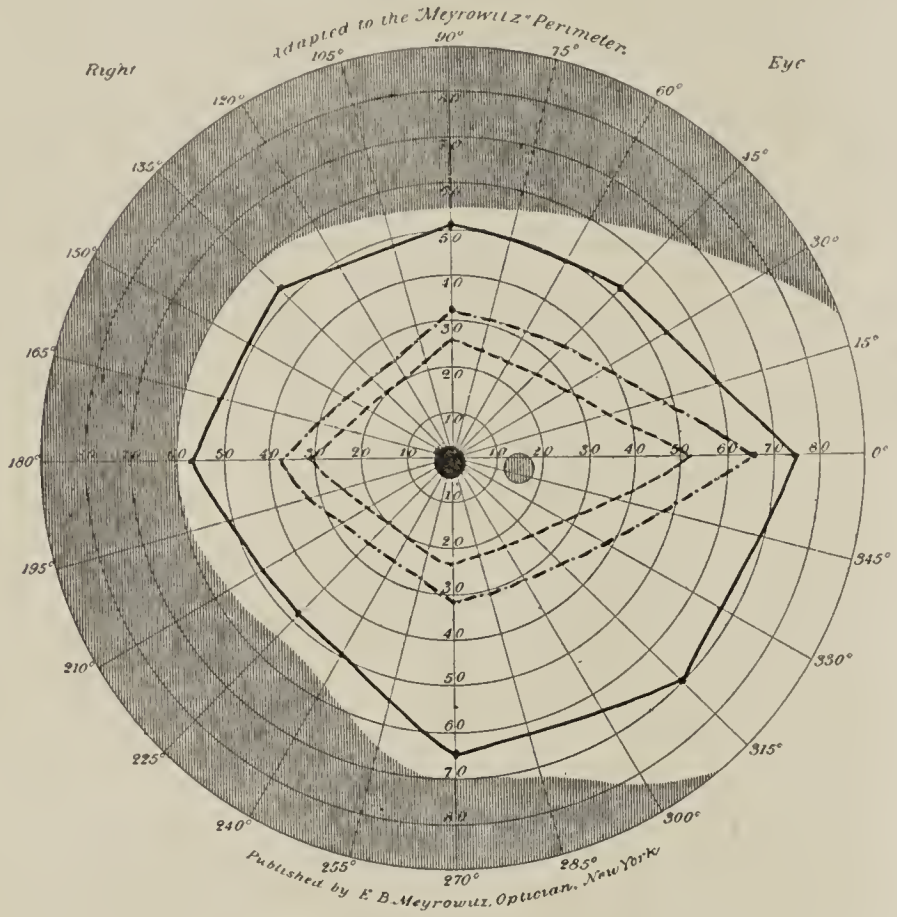

Fig. 1.—Chart October 18, 1910. Showing what was regarded as an indication of practically normal field relations. Note that eight points were relied upon for the form field and only four for both blue and red.

42 cases were admitted with the diagnosis of tumor, and of these in only 3 were fairly careful perimetric charts plotted, the tests for visual defects in the other cases amounting to nothing more than rough finger observations. The results in these cases are therefore negligible.

Since June 18, 1905, to the present writing, January 1, 1911—approximately a period of five years—the 200 cases

[5] Unless otherwise stated on the legends or case reports throughout this series of papers, discs of 0.5 mm. have been used in the making of the charts, and the outer boundary records the form field rather than that for white. We have usually confined our color observations to blue and red. The green field, though occasionally charted, we have found to be less useful for our purposes, and it has not been included in the charts reproduced in this series of papers.

which form the basis of the present report have come under observation, and with only one or two exceptions they have been surgically treated. The rapid increase in the number of these patients may be judged from the fact that 82 out of the 200 have been admitted for treatment during the past twelve months.

It has been possible to plot reliable perimetric charts in 123 out of the 200 patients, 61.5 per cent, repeated observations having been made in the majority of the 123 cases. In the remaining 77 cases of the series no examinations were possible, or records were made which were too cursory to be of value from the standpoint or our present studies. These cases deserve a word in passing.

Cases in Which Perimetry was Omitted or Precluded.—The examination was precluded owing to blindness in 19

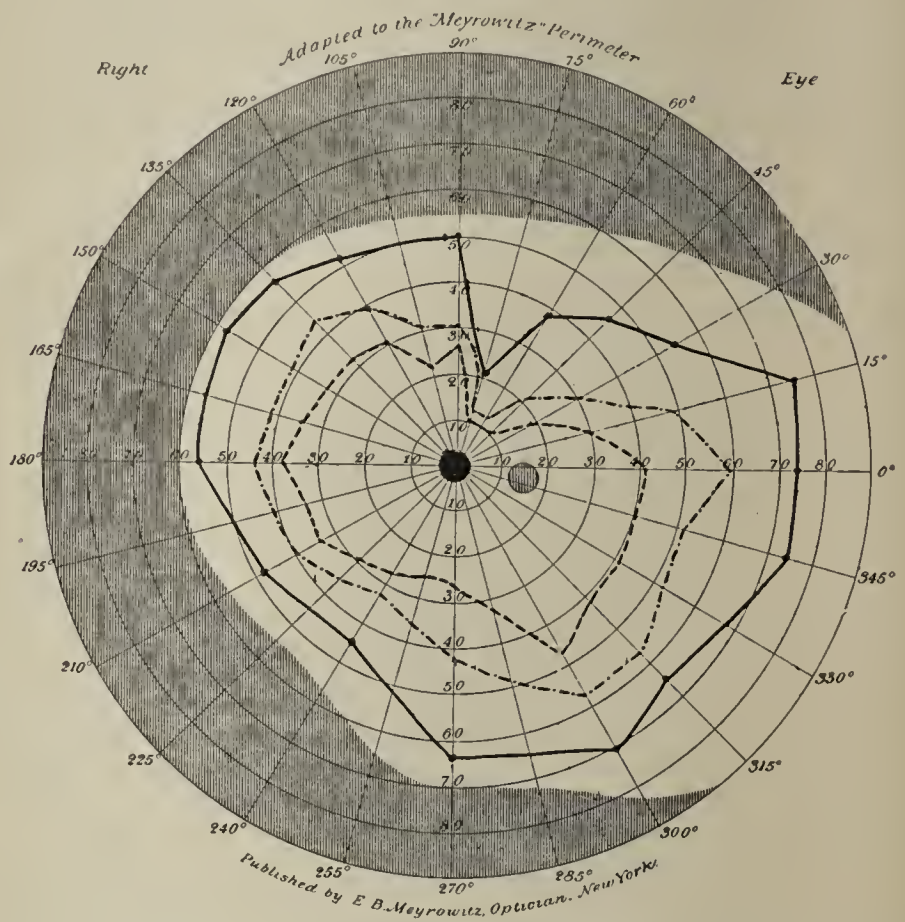

Fig. 2.—Chart October 19, 1910. Corrected chart disclosing upper right temporal defect indicating destruction of some lower fibers of Meyer's loop of the visual pathway in left temporal lobe. Points taken at every 15 degrees for form and nearly as frequently for blue and red. Note the striking difference of color field configuration in the two charts.

cases.[6] The patients were too young to permit of anything more than rough tests in 13 instances. In 28 they were unconscious, aphasic or too ill and having too much vertigo for reliable perimetry, though in a number of these cases subsequent post-operative tests were possible. Nine patients were operated upon out of town, and the fields, if any, which ac-

[6] That 11.6 per cent of all of our cases coming for operation are blind from atrophy secondary to a choked disc is a commentary on the present indecision of physicians in regard to the surgical nature of brain tumors. It is encouraging to note, however, that in the last 100 cases there were only 7 patients who were blind at the time of admission—contrasting favorably with the 12 blind patients in the preceding 100 cases.

company the records were too haphazard to be of value. The same holds true for the records of 9 cases for which we are personally responsible, the fields having been plotted by unreliable observers and not authenticated, or, owing to the exigencies of the case, either neglected entirely or the examination restricted practically to finger tests for form alone.

Cases in Which Perimetry was Possible.—As we have stated, reliable charts were secured from 123 patients. Of this number 27 showed fields which were practically normal in all respects. There remain 95 cases—nearly one-half of the entire number, and 77 per cent of the cases in which the fields could be taken—which displayed abnormalities of diagnostic value. In 42 cases characteristic defects occurred which were definitely of aid in localization. The charts of the other 53 cases showed fairly symmetrical interlacing with more or less tendency toward inversion of the color fields, accompanied by some constriction of the fields for form—an indication of an increase of pressure. These three subdivisions deserve some further analysis.

1. *Normal Fields.*—As stated, these were observed in 27 of the 200 cases (13.5 per cent), and it is interesting to note that practically all of them occurred in the second one hundred cases of the series—an evidence of the growing tendency toward more precocious diagnoses before symptoms have advanced to a high degree. Naturally, normal fields will more often be observed when the tumor primarily involves an area which promptly gives localizing symptoms. This is particularly true of early pontine tumors (2 cases); of many tumors whose first symptom is Jacksonian epilepsy (7 cases); of early intracerebellar or lateral recess lesions (6 cases), and particularly of early hypophyseal growths or hyperplasias which have not reached the point of giving either general pressure or serious neighborhood symptoms (7 cases).

A few of these 27 cases with normal fields showed an early stage of hyperæmia of the nerve-head. This, however, was the exception. In most of them there was neither interlacing nor a suspicion of œdema of the papilla.

The diagnoses of tumors which, on the other hand, originate in relatively silent areas of the brain will naturally depend more often on the existence of general pressure symptoms, important among which are more or less outspoken perimetric deviations. As a matter of fact, the mere enumeration of the percentage of choked discs which have been observed in a given series of tumor cases is apt to mislead; for the figures which are often given, varying from 70 to 80 per cent, depend merely upon the stage of the disease at which on an average the patients have come under observation. And this heretofore has usually been an advanced stage. With the few exceptions of cases in which the growth primarily originates in or near some vital center in the brain stem causing sudden death before general pressure symptoms occur, all brain tumors may ultimately be expected to show a choked disc.

The pontine tumors furnish a good example of this. In the various statistical studies on the occurrence of choked disc as a manifestation of brain tumors attention has been called to the surprisingly low figures in the case of pontine growths. This is naturally accounted for by the fact that from the very situation of the lesion in what may be called the encephalic cross-roads, an early diagnosis is almost certain to be made before pressure symptoms advance to any considerable degree. A tumor of corresponding size in a mute area of the brain would be practically symptomless. Hence it is natural that the existence of a pontine tumor is recognized early, but this does not mean that such a lesion is ultimately any less liable than others to produce a choked disc, except in the case of an early fatality. Indeed, a choked disc would be inevitable in the course of time from compression of the iter and the secondary increase of cerebral pressure due to a ventricular hydrops. The same thing naturally holds true for color interlacing in these cases, and in all of our eight pontine tumors not only choked disc, but color interlacing also—judging from the cases in which it was possible to use the perimeter—has been an inconspicuous or absent feature until late in the disease.

2. *Fields Showing Color Interlacing (Dyschromatopsia).*—Interlacing with more or less inversion and constriction of the color fields was the only perimetric abnormality observed in 53 cases (26.5 per cent of the entire series, 43 per cent of the 123 cases possible to examine). If we add to these 53 cases the 16 in which color interlacing accompanied various types of homonymous hemianopsia there are 69 cases of interlacing in the series. Furthermore, if we deduct from the 123 cases the 27 showing normal fields, and about 20 others with complete loss of color vision (achromatopsia), a constricted form field alone being preserved, it will be seen that the 69 cases which showed interlacing before operation represent about 90 per cent of all those in which this type of perimetric deviation could have been expected. For the cases showing normal fields had not arrived at a stage where pressure was sufficient to produce interlacing; while those with achromatopsia had gone beyond it.[7]

[7] These figures may be compared with the statistics recorded by Bordley and Cushing (*loc. cit.*) two years ago, 50 out of the series of 56 cases then examined having shown color changes. The present figures (69 out of a series of 123 cases) represent a much lower percentage, due partly to the fact that we are seeing tumor cases much earlier in their course than formerly and also to the fact that the proportion of hypophyseal tumors in the series has increased greatly during the past year and has somewhat modified the percentages.

We are aware that many have experienced difficulty in recording color interlacing, and the only corroboration, so far as we know, of our results has been given in a note by B. Sachs (*Jour. Am. Med. Asso.*, 1909, p. 316) and in a report by Byrom Bramwell (*Lancet*, March 5, 1910, p. 631). There are of course other conditions which may produce interlacing, many of them associated with pressure or stasis, as enumerated by de Schweinitz in his chapter on the Psychoses and Neuroses in "The Eye and Nervous System" (Posey and Spiller). We have observed an occasional instance of typical interlacing in exophthalmic goitre.

It possibly should be stated that in plotting the charts the boundary points on each radius are determined for both colors at the same moment. If the fields for blue and red should be plotted separately the relationship of their periphery would be less dependable.

In the 200 cases of our complete series there have been 134 supratentorial (cerebral) and 66 subtentorial lesions, a proportion of two to one. In the group of cerebellar cases more or less symmetrical and bilateral constriction with color interlacing is the only perimetric change we can expect: and of the 53 cases which have shown this change alone without a suggestion of an hemianopic defect, naturally a considerable number proved to be cerebellar (certified or suspected) cases —a proportion of three cerebral to two cerebellar.

Without further analysis of these figures it is apparent that interlacing proves to be one of the most constant of the signs of an increase in pressure, and, what is more important, that it is occasionally the earliest of these signs. In a number of instances, as we have indicated, the condition has preceded a demonstrable choked disc, and, furthermore, when accompanied by a choked disc it has been very commonly observed that the inversion and interlacing disappear after decompression before there is any considerable subsidence of the neuro-retinal swelling. Thus, if this type of dyschromatopsia is to be attributed to pressure it appears to be a more sensitive reaction in many respects than the neuro-retinal œdema itself.

The cases in this group of 53 which showed dyschromatopsia, either in the total absence of a choked disc or in company with a very incipient process, will be recorded in some detail in our second paper. At the same time the perimetric changes observed in the outspoken stages of choked disc will be correlated with Marcus Gunn's five subdivisions of this process based on ophthalmoscopic appearances alone.

3. *Hemianopic Fields.*—Definite field defects other than the mere symmetrical constriction or color interlacing—defects, in other words, which are presumed to indicate direct implication of the visual pathway—have been observed in 42 of the 123 cases in which the examination was possible (33.3 per cent); and it may be said in passing that in a considerable number of the 77 patients in whom the taking of the fields was precluded, the pre-existence of gross hemianopsia of one form or another was indicated by the histories, or the patients may actually have brought suggestive fields taken elsewhere before blindness came on.

In this group of 42 hemianopsias we have included 12 cases of fairly typical binasal hemianopsia. Though the analysis of the cases exhibiting this type of defect will be reserved for the third paper in this series, it may be stated here that in all the condition accompanied an advanced choked disc, often with complete achromatopsia—cases in which merely a constricted temporal field was preserved in each eye. It will be observed that these binasal hemianopsias most often occur in cases of subtentorial growths which have led to a symmetrical change in the two nerves due to secondary atrophy without any direct implication of the visual pathway itself. Thus in considering the prevalence of the true hemianopsias in a given series of intracranial tumors, one should exclude from the list the subtentorial lesions, which are barred from the possibility of direct implication of optic tract and radiation.

In the 200 cases there were 66 (presumable or certified) subtentorial, including pontine, growths; and 38 of these are included with the 123 cases in which the fields were examined. This leaves only 85 cases with cerebral (presumed or certified) lesions subjected to perimetry, and in 30 of them (36.5 per cent) the perimeter has shown what may be interpreted as a direct implication of the visual pathway.

Granting therefore the common occurrence of form and color defects from pressure involvement of the topic tracts and radiation in cerebral tumors proper, of what localizing value are these defects other than to place the lesion in the right or left hemisphere—a simple matter which is usually determinable by other signs? We shall see, however, that the configuration of the homonymous defect is actually of considerable help in determining the situation of the lesion, whether fore or aft and whether above or below the visual pathway in the hemisphere obviously involved.

Our 42 cases of hemianopsia may be subdivided into three main groups: (1) those exhibiting a definite tendency toward a complete binasal loss of vision with some preservation of the temporal fields—the 12 cases of which we have already spoken; (2) those showing a fairly characteristic tendency toward a bitemporal blindness—6 cases; (3) those with an homonymous defect, whether vertically total, quadrantal or, what is far more common, but just as valuable for diagnostic purposes, a fragmentary homonymous constriction—24 cases; and a few illustrations of superior hemianopsia must be included.

Modern decompressive measures for unlocalizable or inaccessible lesions give a definite prolongation not only to the life of the patient, but at the same time to the life of the tumor; and inasmuch as vision under these circumstances should be preserved (and will be unless procrastination has permitted an advanced secondary atrophy) the enlarging growth, if supratentorial, will, in all probability, in the course of time encroach on the geniculo-calcarine pathway. Hence in the future if the perimeter is not neglected we shall doubtless observe among our tumor cases a much larger percentage of hemianopic defects than we have recognized in the past. When we realize the vertical breadth and the antero-posterior course of these fibers it is readily seen that every tumor of the cerebral hemispheres, with the exception of those situated in frontal or superior parietal regions, may at some time in the progress of its enlargement be expected to exert at least some pressure effect on the upper or on the lower portion of the radiation; and whether this shows itself as a beginning homonymous defect in the upper or in the lower part of the field may be of the utmost value from a localizing standpoint.

The hemianopsias which occur as the result of hæmorrhage or softening secondary to vascular disease, are apt to be as sharply cut as they are abrupt in onset, but in the case of tumors the perimetric deviation is a slowly progressing one and is more or less complicated in many instances by the constriction of the fields consequent upon the alterations secondary to an accompanying choked disc. Hence it will be seen when we come to discuss the tumor hemianopsias that the clear-cut vertical meridians which are usually regarded as requisite to the diagnosis of this condition are conspicuously

absent in this series. The condition shown by many of the charts which will acompany the case descriptions represents merely a "tendency toward" an hemianopic defect—suggestive alterations in the field boundaries, in other words, which are as clearly indicative of involvement of the right or left pathway as though the defect were vertically complete. Indeed, these suggestive homonymous or bitemporal constrictions may be registered by defects in the color fields alone, as will be subsequently pointed out.

As the alterations which lead up to the typical hemianopic field defects are progressive, it behooves us to recognize them in their early stages, and the opportunities offered the operating neurologist for a consecutive study of serial fields of patients as their symptoms advance before operation and subside afterward, should give him especial facility in interpreting these states.

Summary.—In a series of 200 cases of brain tumor it has been possible in 123 cases to secure reliable perimetric charts. These have shown (1) normal fields in 27 cases; (2) simple color interlacing or inversion (dyschromatopsia) with more or less constriction, but without other field distortion in 53 cases, and (3) hemianopsia, or a tendency toward this defect, in 42 cases.

NOTES ON NEW BOOKS.

Modern Treatment: The Management of Disease with Medicinal and Non-Medicinal Remedies. By Eminent American and English Authorities. Edited by HOBART AMORY HARE, M. D., Professor of Therapeutics and Materia Medica, Jefferson Medical College, Philadelphia, etc.; assisted by H. R. M. LANDIS, M. D., Medical Director to the Phipps Institute for Tuberculosis and Physician to the White Haven Sanatorium. Two octavo volumes, 1800 pages, with numerous engravings and full page plates. Price per volume in cloth, $6.00. (*Philadelphia and New York: Lea & Febiger, Publishers, 1911.*)

A Handbook of Practical Treatment. In three volumes. By 79 eminent specialists. Edited by JOHN H. MUSSER, M. D., Professor of Clinical Medicine, University of Pennsylvania; and A. O. J. Kelly, M. D., Assistant Professor of Medicine, University of Pennsylvania. Volume 1: Octavo of 909 pages, illustrated. Per volume, cloth, $6.00. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

The appearance of these two works at practically the same time by two of the leading medical publishing houses shows the spirit of competition which exists in this business as well as in so many other active ones. For the moment, Lea & Febiger have the advantage, since both their volumes have appeared, while but two of Saunders Company are as yet published. "Practical Treatment" will in the end be the larger work by nearly 900 pages, as the first volumes of both publications are practically identical not only in size but in general appearance. The similarity between these two publications goes still further, as a few writers have contributed to both systems. There is one rather striking feature in "Practical Treatment," the appearance of a number of articles by surgeons, a feature which, on the whole, seems ill-advised in such a work. The doctor in contradistinction to the surgeon is usually the better therapeutist of the two, and in such works, which are not intended to take up surgical treatment, it seems as if it would have been better to have all the articles written by doctors. Otherwise the list of contributors to both works is well selected, and in purchasing one or the other book there is little to choose. It is six of one, and half a dozen of the other. In two such systems there can be but little difference, when both are ably edited as in this case, except in the arrangement of the articles, a perfectly minor point, for after all whether the treatment of one set of diseases is in the first or second volume is of no consequence, and such differences exist. "Modern" or "Practical" Treatment, call it which you will, is fundamentally the same in America; different practitioners will have slightly varying methods of treatment, but from East to West or from North to South the well-trained doctors practice the same methods generally. Some will not agree on a milk or a more liberal diet in typhoid fever, as to which is the best, or as to the values of hydro-, electro-, and mechanotherapy in various diseases, but none the less the basis of all treatment is the same everywhere in this country at least, and the young practitioner will find the pros and cons for the varying treatments exposed in both systems. So both are to be recommended and both will be found serviceable guides. The articles are all written by well-known practitioners, and differences of opinion as expressed in one or the other work will but serve to stimulate the reader to further thought on his own part.

Inebriety: A Clinical Treatise on the Etiology, Symptomatology, Neurosis, Psychosis and Treatment and the Medico-Legal Relations. By T. D. CROTHERS, M. D., Hartford, Conn. (*Cincinnati, Ohio: Harvey Publishing Company, 1911.*)

No one can overestimate the value to mankind of all honest efforts to solve the social, economical and moral problems which result from alcoholic excesses and addictions; and hence all books like the one under review deserve careful consideration at the hands of the reviewer. The author of this volume has been actively interested for many years in the study and treatment of inebriety and should by experience and knowledge be well fitted to give to the profession much valuable knowledge. The scope of the work is ambitious and the author has collected his material with great industry. The work, however, is not a strictly scientific one, but is rather a popular treatise. The central thought in it seems to be that inebriety is at all times and under all circumstances a physical disease and clinical facts and plausible theories seem to combine throughout the work to establish the truth of it. Unfortunately the evidence to this effect has not always been gathered with the care which seems to meet the requirements of scientific accuracy. Clinical facts are loosely stated and broad generalizations are often made from inadequate premises. Take a single unimportant example which may be cited to show the attitude of the author. He says in speaking of the causes of inebriety: "The evidence from the history of many cases shows that excessive cigarette smoking is followed by inebriety." That excessive cigarette smoking, like many other excesses, is frequently a concomitant of inebriety, is not to be doubted, but it is nothing more than this. What evidence can be produced to establish any causal relation between cigarette smoking and inebriety? The same lack of scientific precision is noticeable in the author's clinical histories which for the most part are dogmatic statements, of conclusions which seem to have been reached oftentimes as the confirmation of previously accepted theories rather than the presentation of clinical data.

As to the author's contention that inebriety is solely a physical disease, many queries suggest themselves. If it is a disease, has it a definite course, well-recognized symptoms and an established method of treatment? The causes of inebriety differ with individual cases. The pathological appearances after death are

not invariable. Many inebriates go down to early death in spite of all efforts to arrest the course of the malady. Others, as the author points out, get well spontaneously; "the craze for alcohol at times dies out of itself from causes unknown," as he expresses it. Inebriety seems a condition characterized by a depressed state of the nervous system due to drink and to other causes often physical, mental or moral, sometimes to all of them combined. The author's remarks on treatment seem judicious and well-calculated to assist the physician who seeks knowledge upon this point. The chapters entitled "Inebriety as Noted in Ancient Civilization" and "Medico-Legal Questions" are of much interest.

Diseases of the Anus, Rectum and Sigmoid, for the use of Students and General Practitioners. By SAMUEL T. EARLE, Professor Emeritus of Diseases of the Rectum in the Baltimore Medical College, etc. (*Philadelphia and London: J. B. Lippincott Co., 1911.*)

Following the custom usual to text-books of this type, Dr. Earle devotes the first chapter of his work to a review of the chief facts concerning the anatomy and physiology of his chosen field. Then a very practical presentation of general technical questions—methods of examination, anæsthetics, equipment, etc.—is given. The first abnormal condition discussed is that ever obtruding subject, constipation; and its forms, causes and symptoms are considered at length. From the limitations of the author's subject, the operative treatment of constipation directed at the intestinal tract oral to the sigmoid receives no attention. It is of interest to note that Earle attaches less importance to lesions of Houston's valves, as a cause of constipation, than certain other proctologists are inclined to attribute to such conditions.

Diseases of an inflammatory nature, embracing such frequently encountered conditions as ulcerations, perirectal abscesses and fistulæ, of course constitute an important division of the subject-matter of such a book, and this general group is handled in a manner sufficiently full, and yet free from the tedious reiteration so often inflicted on the reader. A reflection of the present interest in sigmoiditis and diverticulitis is found in the author's treatment of these subjects. Here and elsewhere in the book, apt and frequent citations from original sources are a noticeably valuable characteristic. Congenital anomalies, fissure, stricture, and pruritus ani, are each the subject of a chapter in which the accepted facts are set forth in a readable way. One naturally does not turn to such a book, specifically addressed to students and general practitioners, for contributions to the advancement of the subject, but rather for a resumé of the present consensus of opinion; nevertheless to many readers, especially to surgeons, perhaps the chief interest of the book lies in the chapter on hemorrhoids, where Earle's own method of operating is described.

Conditions demanding larger surgical procedures, such as prolapsus of the rectum, new growths, and extensive injuries, receive the emphasis to which their importance entitles them, and the text is reinforced by numerous good illustrations. Throughout the book, the writer manifests his interest in the pathology of the various lesions, and numerous illustrations of gross and microscopic specimens are given. The last two chapters, devoted respectively to diseases of the coccyx and Herschsprung's disease, while not strictly within the scope of the work, are so closely allied to it that they require no apology, but distinctly add to the completeness of the volume.

In the preface, Dr. Earle says: "The maladies discussed are very common and very stubborn. My chief care has been to include the most recent and effective methods of cure, and to give these comprehensively and succinctly." In this purpose the writer has distinctly succeeded, as the generally accepted facts and theories are well presented, and there is a noteworthy absence of the repetition of commonplace case-reports and details of technique so frequently encountered. At the risk of seeming captious, one might wish for a more definite ring of authority in some places, and another minor point for criticism is afforded by occasional involved sentence-construction which somewhat obscures the meaning. On the whole, however, the book fulfills the purpose for which it was conceived very well. A touch of personal interest to the Johns Hopkins Medical School men lies in the dedication of the book to Dr. Councilman and the citation of opinions of Dr. Welch, with both of whom Dr. Earle worked as a post-graduate in pathology.

Differential Diagnosis. Presented through an Analysis of 383 cases. By RICHARD C. CABOT, M.D., Assistant Professor of Clinical Medicine, Harvard Medical School. 753 pages, illustrated. Price, $5.50. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

The use of groups of cases, each group presenting a distinct symptom, as cough, fever, localized pain, chill, coma, convulsions, weakness, etc., as a basis for a work on differential diagnosis is a new and clever one of the author, and is bound to be most serviceable to many students. It is similar to a clinical conference, where the instructor has gathered a number of patients together who show a more or less common condition, and then differentiated their troubles to his hearers. Those who will use this book intelligently, and before reading the discussion of the cases presented, will try to analyze them for themselves, and then compare their own diagnoses with those of the author, will put themselves through an excellent training. They should first read the introductory pages to each symptom and thus have an anatomical and physiological ground to build upon. There may be errors, as the writer suggests, in his work, but it will only be a brilliant student who will find them, and others will make no mistake in accepting the diagnosis of the author. The work is to be heartily commended as a fresh and attractive method of teaching, and its success will be watched with much interest.

The Blues (Splanchnic Neurasthenia). Causes and Cure. By ALBERT ABRAMS, M. D., etc. Illustrated. Fourth Edition. Revised and Enlarged. Price, $1.50. (*New York: E. B. Treat & Co., 1911.*)

The only difference between this edition and the preceding one lies in a brief note amplifying the treatment for this condition. The author believes that concussion of certain of the spinous processes will reduce congestion in the abdominal organs, and so cure "the blues." It would be most fortunate for the human race were this mental condition always due to a physical condition so easily alleviated!

Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, Rochester, Minnesota, 1905-1909. Octavo of 668 pages, illustrated. $5.50 net. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

All of these papers have appeared in various medical journals, and gathered together in a handsome volume, there is much of interest in them. Most doctors, who have not been to Rochester, think of the "Mayo Clinic" as being the two brothers Mayo, but in the list of contributors to this volume there are fourteen names—an indication of what a large clinic exists under this name, and the extent of the work carried on there.

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THE CHANGES IN THE CIRCULATION IN AORTIC INSUFFICIENCY.

By William G. MacCallum, M. D.,

Professor of Pathology, Columbia University.

(*From the Department of Pathology, Columbia University, New York.*)

In the case of lesions of the aortic valves, which cause them to be insufficient, there occur certain well known symptoms which are perhaps more characteristic than those following any other valvular lesion, and have been very minutely studied. Particularly striking are the collapsing pulse and the diastolic murmur with the hypertrophy of the heart, and especially of the left ventricle which follows. Ordinarily these things have been explained as being due to the regurgitation into the left ventricle of a portion of the blood thrown out at each systole, and this explanation has generally been regarded as satisfactory until recently when H. A. Stewart[1] in a study of this condition brought forward the problem as to the real cause of the fall of pressure therein and the significance of the position of the dicrotic notch in the pulse curve.

Of course when the heart has become hypertrophied, different conditions may prevail, and so, too, when other lesions of the heart or of the arteries exist, the simple impairment of the circulation resulting from the lesion of the aortic valves is obscured. It is necessary, therefore, to study the effects of aortic insufficiency produced in a normal animal, and this can easily be done, as in the work of Stewart, by tearing a segment of the valve with the valvulotome described in an earlier paper.[2]

[1] Stewart: Experimental and Clinical Investigations in Aortic Insufficiency. Arch. Int. M., January, 1908.

[2] MacCallum: Johns Hopkins Hosp. Bull., August, 1906.

Stewart confirmed the statement of Mackenzie, Broadbent and others that the dicrotic notch holds a position very low in the descending arm of the pulse wave, when there is aortic insufficiency, whereas it is normally above the middle of this slope. Since the dicrotic notch is normally found to be synchronous with the end of the systole, and since the dicrotic notch in aortic insufficiency occupies a position approaching the trough of the pulse wave, he concludes that the collapse occurs for the most part during the latter part of the systole. There can therefore be no regurgitation during that time and the collapse must be due to widening of the arteries and ready escape of the blood. A similar position is occupied by the dicrotic notch in the pulse of low arterial pressure. If the pressure is raised by compressing the aorta or by giving adrenalin, or, if from the existence of arteriosclerosis, the pressure is high, the dicrotic notch even in aortic insufficiency assumes a higher position and the pulse is no longer regarded as collapsing.

Further, since the diastolic arterial pressure is found to fall on the tearing of the aortic valve, while the systolic pressure is maintained, he argues that there must have been an attendant vasodilatation. Since the pulse pressure has been increased because of the fall in diastolic pressure, it can only have resulted from peripheral dilation.

Such a dilation of the peripheral vessels must constitute a protective adaptation which instantly comes into play upon

the tearing of the valve and must be brought about by vasomotor influences. Since this seemed at first sight hard to accept in place of the time honored explanation on the basis of regurgitation, I have examined it more closely. In order to approach these conditions I have devised an arrangement of the circulation, which I find, on looking over the literature, is somewhat like that used by Martin,[3] Howell and Donaldson,[4] excepting in that it does not interfere with the nervous connections of the heart, and is, on the whole, more manageable. I have also found the description of a somewhat similar device by Lohmann[5] in a recent journal.

It is as follows, the aim being to eliminate as far as possible the influence of the vasomotors and to determine directly the output of the aorta in relation to that of the ventricle. In devising a method which will give us the output of the heart under controlled conditions of peripheral pressure we must begin, I suppose, with the idea that such results may not correspond absolutely with those in the normal intact animal, but that when carefully measured before and after the insufficiency is produced, they will give us a clear idea of the changes which depend upon the insufficiency. This is all that one can claim for the results which follow, although as a matter of fact it seems perfectly easy to reproduce under such conditions a state of the circulation indistinguishable from that of the normal animal.

The method used will be made clear by the accompanying diagram (Fig. 1.) In order to eliminate the effect upon the heart of a peripheral resistance such as is offered by the systemic arteries, liable to constant change and difficult to measure and change at will, the aorta is cut through at the arch and connected with a canula and a long rubber tube with a curved glass outlet of the same caliber. This outlet can be set at any height upon the graduated vertical rods. A cistern supported at the same height and movable with the outflow nozzle, contains defibrinated blood usually mixed with Ringer's solution, which, after passing through a coil immersed in warm water, runs through a second canula into the distal portion of the aorta. Naturally, the first blood which escapes will clot and is not emptied into the cistern until it has been defibrinated; but after a short time all the blood in use has become defibrinated and the outflow nozzle may be turned so as to empty directly into the cistern. Then the circulation will go on indefinitely, differing from the normal in that it drops through the open air at one point and there may be caught and measured, and in that the variable peripheral arterial pressure is replaced by an outflow level which may be precisely controlled by merely moving the supporting clamp up and down on the graduated standard. Any necessary manometers may be attached laterally to the rubber tube which represents the aorta. A plethysmograph constructed after the manner of Henderson's but made in a more suitable shape, and of glass so that the heart can be seen, is put upon the heart and connected with a tambour whose movements have been calibrated. This plethysmograph is put into exactly that position in which it allows the heart to lie naturally and then fixed there with a clamped support. Its lower surface is made nearly flat so as not to dislodge the heart nor press upon the great veins.[6] The outflowing blood is caught in a graduated glass cylinder and as the level of the blood rises in the cylinder each 10 cc. is recorded by an electric signal writing on the same drum as the manometers and plethysmograph. All of these pens are exactly superposed.

The table, the height of which can be raised or lowered by a screw, is adjusted so that the heart is on a level with the zero of the graduated uprights which run nearly to the ceiling of the room. Pressure is then estimated in centimeters of blood although it is, of course, easy to read it off in millimeters of mercury from the curves. A Jacquet chronograph accompanies the manometers.

It is clear that a constant error is involved in estimating the total output, because although the subclavian arteries can be ligated, the carotids must be left open. Of course, one might arrange a separate circulation for the head, but the error is constant enough to make little difference in the result obtained. It involves a constant difference between the estimated value of the plethysmographic excursion and the measured output per beat. Part of this may be residual blood, but part is blood escaping into the carotids.

In introducing the canulas into the aorta it has been found advisable to open the subclavian artery and allow free bleeding while the aorta is clamped in order to relieve the strain upon the heart. When the animal is thus arranged, the pressure against which the heart expels blood into the aorta is determined by the position of the outflow tube. The pressure of the blood entering the distal portion of the aorta, and consequently the amount of blood finally supplied to the heart, depends upon the height at which the cistern is placed. If the cistern is maintained at a constant height and the outflow tube moved up and down, it is found that the actual output of the heart through the aorta is changed but little by the alterations in pressure, as pointed out by Howell and Donaldson. It seems, however, that when the cistern stands far above the outflow tube, a certain amount of blood must run through the animal to the outflow by the force of gravity.

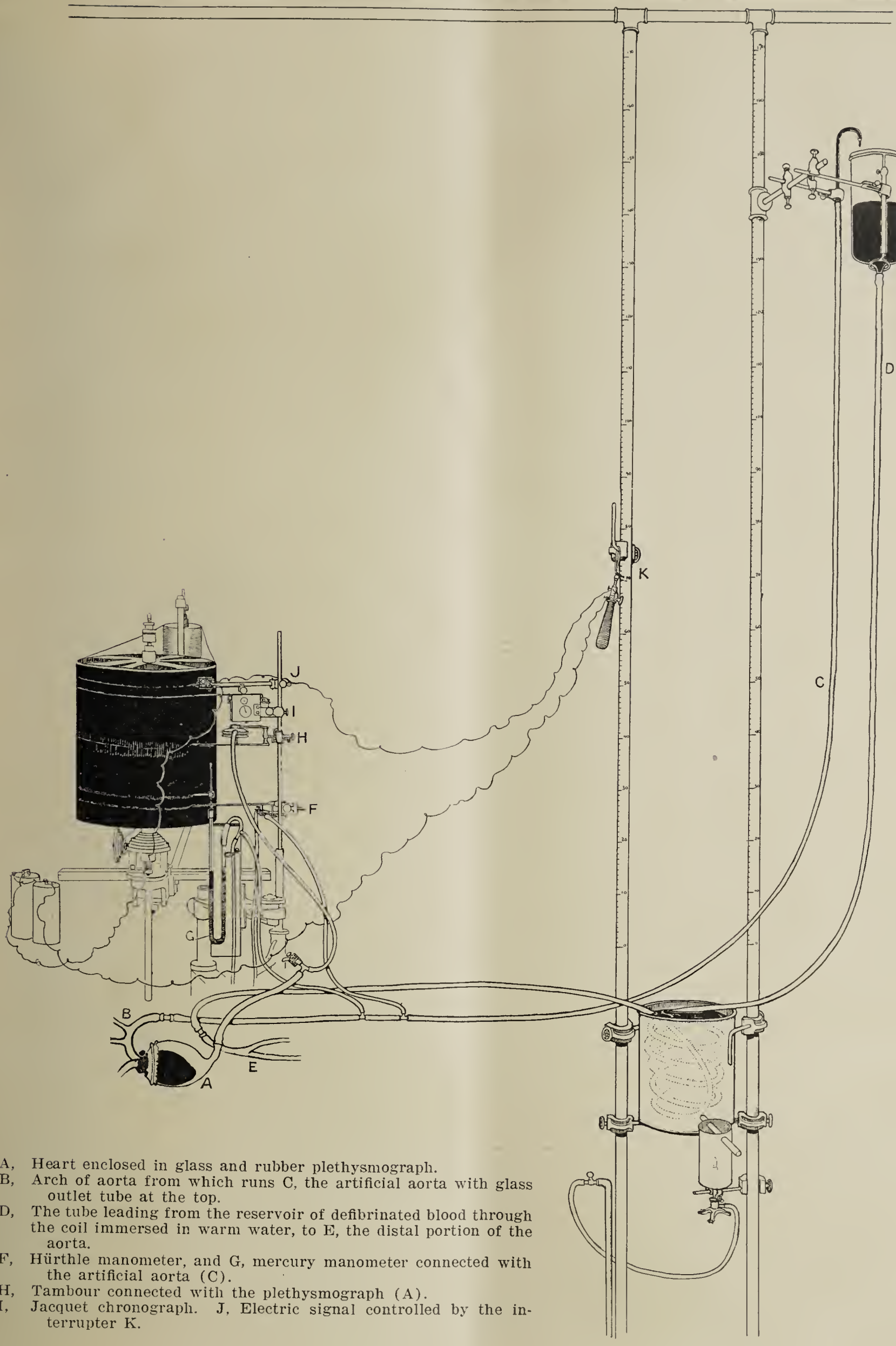
Ordinarily the elevation of pressure in the intact animal is produced by narrowing the arterioles which would undoubtedly tend to affect the amount of blood entering the veins; but apparently this is exactly compensated by the increased force and consequent rapidity with which the heart sends the blood through the narrow channels and the circulation proceeds as

[3] Martin: Philos. Trans. Roy. Soc., 1883, p. 663.

[4] Howell & Donaldson: Philos. Trans. Roy. Soc., 1884, part 1, p. 139.

[5] Lohmann: Pflüger's Archiv, 118, 1908.

[6] The tambour of the plethysmograph may be calibrated, of course, by attaching it to a flask into which a burette allows fluid to drop 1 cc. at a time, but it is much more readily and exactly done with a syringe. One cc. or 5 cc. of water is expelled from the syringe into a graduate and the ring on the piston rod then screwed down tight on the top of the syringe. After this the excursion of the piston is 1 cc. or 5 cc. as arranged and it is quite easy to communicate this to the tambour. It can be done rapidly and produces a curve like that obtained from the heart.



A, Heart enclosed in glass and rubber plethysmograph.
B, Arch of aorta from which runs C, the artificial aorta with glass outlet tube at the top.
D, The tube leading from the reservoir of defibrinated blood through the coil immersed in warm water, to E, the distal portion of the aorta.
F, Hürthle manometer, and G, mercury manometer connected with the artificial aorta (C).
H, Tambour connected with the plethysmograph (A).
I, Jacquet chronograph. J, Electric signal controlled by the interrupter K.

before. So, too, it is found that if the cistern and outflow tube are kept at the same level, the outflow and inflow are about constant and thus probably resemble more closely the conditions in the intact animal than when the inflow is kept constant and the level of outflow changed. Nevertheless, both conditions were studied in many curves.

When the level of the cistern and of the outflow were the same, the elevation of these increased the rate of the circulation. The amount of blood thrown out of the aorta per beat increases with the elevation; consequently, the amount of blood handled by the ventricle increases, the ventricle dilates and its excursion increases. It not only relaxes to a greater degree, but it contracts and empties itself completely. Thus the plethysmographic curve not only shows an increased excursion, with heightened pressure of this sort, but occupies a position further below the base line. This is the usual criterion of the tone of the ventricle, but if we disregard the conditions of malnutrition of the myocardium, of which we shall speak later, it seems that such accommodative dilatation, associated as it is with an improved excursion and the easy performance of increased work, should hardly be referred to as a diminution of tone. This, however, is a question of definition, and we hope to say more at another time of the question of tone. In practice, the plethysmograph was opened at each change of pressure so that its excursions, when again closed, were executed directly about the base line. In this way, calibration is less complicated and the disturbing element of the compression of the air in the plethysmograph was eliminated. When this was not done, however, it was found that at a pressure of 150-200 cm. of blood, the heart would make very great excursions at a level far below the base line, ejecting blood very rapidly, while at low pressures the heart became very small and made small excursions at a level far above the base line with relatively slight output of blood (Curve I). This seems to be chiefly dependent upon the amount of blood handled, for when the cistern was kept at a constant level, the excursions varied far less.

The character of the normal pulse may be studied in the curve of the Hürthle manometer taken from the aorta laterally. It might seem that the substitution of gravity for the resistance offered by friction in the arterioles might produce fallacies in the interpretation of the pulse curve, but after all, the elasticity of the arteries, represented here by that of the rubber tube, is the only force which forms the pulse aside from the peripheral resistance and the impulse from the heart. As a matter of fact, experiments were made to test this both in the normal intact animal and in those in which aortic insufficiency had already been produced, and it was found that the pulse curve, after the cutting of the aorta and the establishment of the new arrangement, was indistinguishable from that of the intact animal of five minutes before, as may be seen in the accompanying curves (Curve IX).

It might be thought that in the intact arterial tree it would be easy for the elastic contraction of the artery to continuously propel blood along into the veins, whereas in the upright rubber tube, the expulsion must depend upon the impulse of the heart alone; but a moment's reflection will show that with the cessation of the systolic impulse and the escape of blood over the level of the outflow, the level of the blood is still exactly there, and if the elastic tube is overdistended its recoil will drive more blood over, precisely as in the case of the arterial tree with its capillaries.

The pulse curve shows the dicrotic notch and wave precisely as in the intact animal. The position of this notch changes with changes in the level of the outflow, being low on the slope when the outflow is low and rising toward the summit of the primary wave, as the outflow tube, and consequently the pressure and tension of the wall are elevated.

It is difficult for me to believe that the form of the pulse wave can be directly dependent upon the rapid escape of the blood from the arteries. If the tube into which the heart ejects blood is elastic, and of any considerable length, even if it be widely open at its end, it will require an appreciable time for the blood to pass along and escape, and it seems probable that even in such a case the pulse wave will reach the end of the tube before the actual mass of fluid, the injection of which produced that pulse wave, does so and escapes.

Even if the elastic tube be of uniform caliber throughout, I do not believe that the form of the systolic pulse wave could be affected by the actual escape of the fluid, for it is certainly formed before that, if the tube is of any considerable length. To attain such a condition, the aorta would require to be like a very short, very widely open straight tube with rigid walls. Far less, then, does it seem possible that the arterial tree as it exists could afford such conditions even with the maximal conceivable dilation of the arterioles.

On the other hand, although it cannot be conceded that the systolic quantum of blood could get out of the way rapidly enough to produce a change in the form of that systolic wave (since the wave is an expression of pressure and not of the movement of fluid), it is obvious that its rapid removal will leave the vessel partly empty with relaxed walls when the time arrives for the next systolic impact; and it is this relaxed condition of the wall, I think, which causes the peculiar form of the pulse in aortic insufficiency.

Stewart has explained, on the basis of the work of Haycraft, Lewis, Roy and others, how the collapsing character of the pulse is dependent upon a low diastolic pressure, high systolic pressure and therefore high pulse pressure not being necessary. I may quote a paragraph: "From the figures given by Roy of the extensibility of the arterial walls at different pressures, two pulse curves are drawn (Fig. 35). In both instances the excess of systolic over diastolic pressure is the same, viz: 60 mm. Hg. but they differ in that in one the diastolic pressure is below normal, viz: 50 mm. Hg. while in the other it is somewhat above normal, viz: 80 mm. Hg. In the lower curve the amplitude is double that in the upper, the angle between the upstroke and downstroke is more acute, and the dicrotic notch relatively lower. In the upper curve, upstroke and downstroke are oblique and the angle between them is widened. In the curve taken at the low pressure there is more movement of the arterial wall for the same change of pressure. The one

would be classified as a "collapsing" pulse, the other as "sustained."

It seems that with low pressure the amplitude of the pulse is increased chiefly by the facile yielding of the lax wall of the incompletely distended artery so that the relative position of the dicrotic notch is due to the increased excursion of the vessel wall above that point in the curve at which the end of the systole is indicated by the dicrotic notch.

It can be readily shown that the actual amount of blood which escapes when the heart is working at a low pressure is less than that when the heart pumps against a high pressure because the amount supplied to the heart is less. In other words, the rate of the circulation becomes greater at the higher pressure, at least up to a certain optimum, but this seems to have nothing to do with the character of the pulse except in that, at the high pressure, the walls of the artery are under high tension while at a low pressure they are lax. At high tension the systolic pressure would not be able to expand the vessel so far by its sudden impulse before the closure of the valves and therefore the dicrotic notch would appear after only a slight systolic fling, whereas if the pressure during diastole is low and the walls of the vessel lax, the same systolic impulse

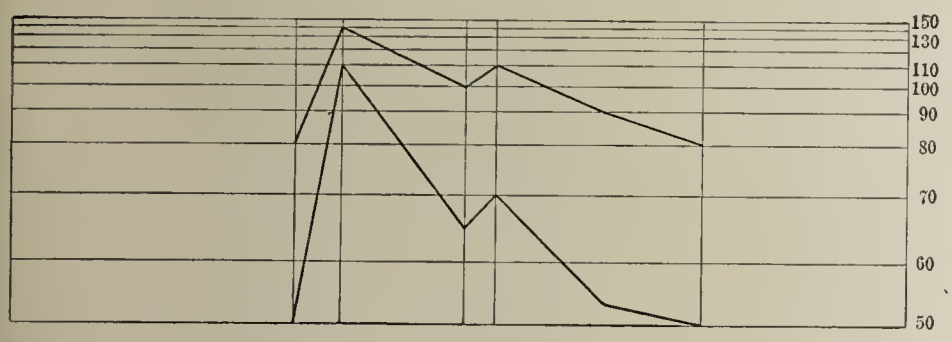


Fig. 35.—Diagrammatic representation of two pulse curves indicating the same pulse pressure, but at different diastolic pressures. The horizontal lines indicate the extensibility of the artery at given pressures (after Lewis).

would produce a considerable fling before the dicrotic notch which would therefore stand relatively low on the downward slope. Measured from the trough of the wave the dicrotic notch might stand equally high in a collapsing and a non-collapsing pulse, but in the collapsing, the excessive excursion above this would make the dicrotic notch relatively low. This is especially strikingly seen in the tremendous collapsing pulse which occurs when the heart is dying from inadequate coronary circulation. The slow but violent systoles throw a quantity of blood into the relaxed almost empty artery and a great fling results before the dicrotic notch.

This gives a ready explanation of the change in the character of the pulse when the aorta is compressed or adrenalin given. These measures increase the tension of the arterial wall by preventing the outflow and it is this increased tension which changes the form of the pulse. In the case of arteriosclerosis in which aortic insufficiency is said not to produce a typical collapsing pulse, it seems more probable that the rigidity of the artery wall prevents its being distended by the systolic impulse even more effectively than a heightened tension could. As a matter of fact while in the pulse curve of aortic insufficiency produced by tearing the valve the dicrotic notch may be quite high on the downstroke of the curve if the pressure is maintained at a fairly high level, it is often very indistinct and one receives the impression that the imperfection of the valves prevents its proper formation.

In the arrangement of the circulation described, the position of the outflow tube determines in a way the pressure. As long as the tube is full to the outflow level, that level represents the diastolic pressure. If the valves are intact the heart responds and maintains the level, but if its nutrition suffers, it dilates and the blood level falls rapidly in the tube. If the aortic valves are torn, the level is maintained but by more active work on the part of the heart. The systolic pressure rises above this, dilating the tube as shown by the summit of the pulse wave which passes along to the outflow.

If, in the animal with an artificial aorta, the outflow tube be set at any level and aortic insufficiency be produced, the pulse pressure instantly becomes greatly increased. There is nothing to represent the supposed accommodative widening of the peripheral vessels here and the outflow from the end of the tube per beat is practically always just what it was before, but still there is greatly increased pulse pressure both from systolic elevation and diastolic fall. The only possible explanation of this is the existence of regurgitation. This relaxes the tension of the wall of the vessel which then receives with the next systole the regurgitated blood together with the normal output. Since the amount of the regurgitated blood again sinks back, the actual outflow is the normal; but the impact of the whole mass thrown out by the heart on the relaxed arterial wall gives the collapsing character of the pulse wave, and the fall in the diastolic pressure must be due, not to a peripheral escape, but to an escape into the heart.

If the level of the outflow tube is high and a high systolic tension thus allowed, the systole will take place into a tube already tense—no great fling or sudden distension will be produced before the end of systole and the dicrotic notch will therefore be at the bottom of only a relatively small part of the downward slope. If the outflow tube be at a low level, less blood will reach the heart from the low cistern, less effort will be made to handle it, less will be thrown into the vessels whose size and elasticity are constant, and the lax wall will be given a fling which leaves the dicrotic notch low.

Another possible explanation of the position of the dicrotic wave lies in the fact that when the valves are torn they can hardly give rise to such a sharp wave or notch and that it may well be that the recoil is from the wall of the ventricle rather than from the valve. Indeed, in many of the curves of extreme insufficiency, it is difficult to discern anything of the dicrotic wave at all. This is especially suggested by the auscultation of the murmur, for although, of course, any such method must be inexact, one is much inpressed by watching the formation of the curve in a slowly beating heart with low dicrotic notch or hyperdicrotism following aortic insufficiency with the finger and the stethoscope on the heart. The murmur starts precisely with the end of the systolic heave and persists through the

downward slope to the trough or notch where it stops—the hyperdicrotic wave is executed in silence and then begins sharply the new systole (Curve VI).

On the whole, it seems that the position of the dicrotic notch is chiefly a question of the tension of the vessel wall. Similarly the collapsing quality of the pulse must be a question of the incomplete filling of the aorta just prior to systole and the consequent fling of its lax wall by the injection of the systolic quantum.

I can readily understand that long continuance of this condition might widen the arteries and thus possibly account for the capillary pulse which would be the more easily brought about by the impulsion of an excessive quantity of blood into the aorta even though that blood never reached the periphery. Indeed it is not hard to believe that with hypertrophy of the ventricle the blood might be sent more rapidly through the veins. *But all of these things are the final effects of the changes resulting from aortic insufficiency and not their causes.*

By means of the rearrangement of the circulation with the artificial aorta, it is possible to arrive at some mathematical conclusions as to the exact nature of the mechanism of the blood flow in aortic insufficiency, for it is easy to estimate the output from the aorta at each beat of the heart and at the same time to measure the output from the ventricle as calculated from the calibration of the plethysmographic tracing. When the valves are intact, these two figures are not far apart. A constant error lies in the escape of blood into the carotids, and nothing more than a comparison of the relations before and after insufficiency is attempted. When the valve is torn, it is found that the systolic pressure as shown by the manometers is maintained. The diastolic pressure sinks, the output per beat or at least per minute (for the rate may change and become slower) is about the same, the plethysmographic curve maintains its level or stands a little higher—its excursions are greatly increased in amplitude. These things are true of the artificial aorta and I find them true also of the animal with intact aorta, although Dr. Stewart finds no marked increase in the plethysmographic excursion. In a few experiments made to determine this point I have found an increased plethysmographic excursion exactly as in the cases with the aorta cut.

It must be borne in mind, however, that if there be regurgitation into the ventricle, the amount of blood actually circulating round to the heart will tend to be less than normal, while the volume of the left ventricle will be increased by the reception of the regurgitant blood. The volume of the right ventricle, will, however, be correspondingly decreased on account of the smaller amount of blood it receives. Such a combination might conceivably proceed without on the whole any enlargement of the heart and in that way account for the high level of the plethysmographic curve.

Before the insufficiency, the amount expelled per beat from the aorta nearly equals that put out by the ventricle, but immediately upon tearing the valve there arises a great discrepancy. The excursion of the cardiac plethysmograph becomes much greater, showing a much larger output, while the aortic delivery remains practically unchanged—undoubtedly therefore, at each beat a considerable quantity of blood is thrown out of the heart into the aorta which never reaches the outflow orifice. It must go back into the heart and be thrown out again in the same futile way at the next systole. Even at such low pressures as 30 mm. Hg. this "residual" blood may be three times as much after the lesion as it was in the normal heart at pressures of 60 or even 100 mm. Hg.

There is thus a considerable regurgitation, and when a regurgitation of 1 or 2 cc. is spoken of in a dog it is by no means insignificant, for repeated studies of the output per beat at normal pressures in dogs show that quantities such as 10-12 cc. per beat are far too great and that the dog's heart actually puts out quantities nearer 2 cc. per beat when the dog weighs 7 or 8 kg.

The estimation of the work of the heart at any given level of aortic pressure as the product of the plethysmographic excursion and the rate shows us that there is a sudden great increase when the aortic valve is cut. Thus, in one experiment in which the pressure in the aorta was 120 cm. of blood, the work of the ventricle per minute was represented by 348.4 cc. of blood as compared with 220.9 cc. before the valve was torn, although the actual output from the aorta during this time was only 228 as compared with 203 while the heart was intact. This difference is evidently to be accounted for entirely by the regurgitation of the blood and the hypertrophy of the ventricle is, in the same way, easily accounted for as the result of the excessive amount of useless work put upon the ventricle by the imperfection of that mechanism which normally secures and renders permanent the effect of each contraction.

Positive efforts to make clear the nature of the collapsing pulse may easily be made with this modified arrangement of the circulation. It seemed possible that the mere excess of blood from whatever source which the ventricle was called upon to handle, might stimulate its walls to more violent contractions and thus heighten the pulse pressure. To test this, blood was led from another cistern at a rather higher pressure into the left ventricle through a glass tube which was introduced in one instance through the subclavian artery and between the aortic valves in a heart in which no valve had been torn, and in another experiment on a normal dog the extra blood was brought into the ventricle through the same sort of tube which was introduced through the auricular appendix and the mitral orifice into the ventricle. In both cases the valves closed snugly about this tube and there was no leakage. In both experiments the result was merely a slight elevation of pressure and a considerable increase in the aortic output (largely due, no doubt, to gravity). Nothing of the collapsing character appeared in the pulse.

On the other hand, when the tube passing into the left ventricle was led, not from a separate blood reservoir at a high level, but from any point along the side of the artificial aorta which was tapped with the aid of a "T" tube, the pulse instantly assumed the collapsing character when the artificial regurgitation was allowed, and as suddenly stopped and returned to normal when that tube was clamped. Undoubtedly

this experiment reproduces in the normal heart the principle of regurgitation which is shown in the heart with a torn aortic valve. In this curve the height of the dicrotic notch will correspond roughly with the level at which the aorta is tapped.

Again, if in an experiment in which a collapsing pulse has been produced by tearing the valve, we introduce an artificial valve into the tube which represents the aorta, the pulse will lose its collapsing character, and the more perfectly the valve acts the more nearly will it approach the normal form.

From all this it seems unavoidable to conclude that regurgitation plays a predominant part in the whole complex of aortic insufficiency. The ventricle throws out a quantity of blood into the aorta, which is more than naturally emptied and relaxed by the regurgitation of the previous diastole, thus giving a great fling to the loose wall. Much of the blood returns to the ventricle being in fact only churned out and back from the ventricle. Still, so great is the new effort that a normal or nearly normal amount of blood may be discharged from the aorta. The great pulse pressure produced in this way is very characteristic and since it persists at all pressures it would seem to constitute a specially good criterion of the condition. The dilatation of the peripheral capillaries at each pulsation must be due to the same projectile form of systolic filling of the relaxed vessels.

CONCLUSIONS.

1. By means of the arrangement of the circulation described, it is possible to estimate the work of the ventricle and to study the influence of various factors upon it.

2. The tearing of an aortic valve producing an aortic insufficiency causes the heart to perform an extraordinary amount of work, part of which is devoted to the maintenance of nearly a normal rate of flow on the vessels, while the remainder is expended upon the forcing out of a quantity of blood which each time regurgitates through the torn valve.

3. This extensive and violent excursion of the ventricle together with the effect of the regurgitation produces a very great pulse pressure with low diastolic pressure and the low tension of the arterial wall allows a great systolic fling which occupies a relatively large part of the height of the pulse curve and thus causes the dicrotic notch to occupy a low position which is another characteristic of the collapsing pulse.

The following protocols will show the character of the results obtained by measurements and may be compared with the corresponding curves in so far as they are reproduced. It must be emphasized that the figures have practically no absolute value. An approximate idea of the output of the aorta at varying pressures is obtained but there are many sources of error. So, too, the results obtained by calculation from the calibration of the excursions of the plethysmograph seem to me of very doubtful absolute value. It is possible to change the excursion so greatly by the slightest movement of the plethysmograph or by the slightest inaccuracy of the adaptation of the rubber to the auriculo-ventricular sinus that any arbitrary uniform calibration would seem to me as valuable as the particular factor which is found by calibrating the tambour. Although this is so, when the plethysmograph is once fixed immovably in place the relative values before and after the valvular lesion is produced are perfectly trustworthy, and although as absolute figures they may mean nothing, they give a perfectly good indication of the changes which ensue upon the tearing of the valve. In considering these figures allowance should have been made also for the fact that under such abnormal conditions the size of the two ventricles does not vary equally, so that while in the normal heart an increased flow of blood into the heart might mean an equal enlargement of the ventricles, such an effect might be modified in the heart with torn aortic valve, by the fact that an increased regurgitation would cause a disproportionate enlargement of the left ventricle. This would accentuate the modifications of the "residual blood" which are given in the protocols in which no such allowance is made.

Further, it will be seen that the malnutrition of the heart muscle which follows the severer insufficiencies, may be enough to cause the rapid dilatation of the heart and the death of the animal. In such cases the results are quite different from those in which the heart maintains its activities and one of them is given as an illustration (Table IV). Another (Table III) shows a milder degree of the same thing as the curve progresses and shows also the compensation that may take place when the lesion is merely a hole in the valve by the filling of the hole with clot.

The principles outlined in the above discussion are, however, shown to be true in all the curves if allowances be made for the disturbing effects of malnutrition of the heart muscle.

TABLE I.—February 23, 1911. Normal dog. Wt. 10 kg.

Peripheral pressures	70 cm.	150 cm.	150 cm.	150 cm.	70 cm.
Pleth. swing	18.75	24.	27.5	31.	15.
Calibration	.158÷2	.079=1	mm.		
Estimate	1.48	1.896	2.172	2.449	1.185
Pulse rate	180	225	240	240	220
No. of beats to give 10 cc	10.3	5.87	5.5	6.5	10.5
One beat gives	.97	1.703	1.818	1.538	.952
Residual blood	0.51	.193	.354	.911	.233
Aortic output per minute	174.6	382.5	436.3	369.12	209.4
Heart work per min. (Pleth. x rate)	266.4	526.6	521.2	587.7	260.7

The table shows the changes in the work done by a normal heart with changes in outflow and inflow pressure.

TABLE IV.—January 3. Dog, weight 8.7 kg. Inflow and outflow at 62 cm. Extreme injury, death from dilation.

	Normal.	Aortic insufficiency.
Pleth. swing	12	15
Calibration	.158=1 mm.	divide by 2=.079
Estimate	.948	1.185
Pulse rate	170	120
No. of beats to give 10 cc	17	22.7
One beat gives	.588	.440
Residual blood	.360	.745
Aortic output per minute	100.	89.4
Heart's work per min. (pleth. x rate)	161.16	142.2

TABLE II.—December 23. Outflow 57 cm., inflow 75 em.

	A	B	C	D	E	F	G	H	I
Plethysmographic swing	12.	26.5	31	35	35	33	32		
Calibration	1 mm	= 0.1584 cc.	Each result	is divided b	y 2 for left	ventricle.			
Estimate	.9504	2.0988	2.455	2.772	2.772	2.613	2.534		
Pulse rate	240.	120	90	90	95	95	110	120	120
No. of beats to give 10 cc	23.4	10.6	7	6.65	7.46	7.4	8	15.85	16.8
One beat gives	.427	.943	1.428	1.504	1.340	1.351	1.25	.63	59
Residual blood	.523	1.155	1.027	1.268	1.432	1.262	1.284		
Aortic output per minute (rate x beat value)	102.48	113.16	128.52	135.36	127.30	128.34	137.50	69.3	70.8
Heart work done per minute (pleth. x rate)	228.	251.8	220.9	249.4	263.3	248.2	278.7		

The table shows the effect of the production of aortic insufficiency just before B.

TABLE III.—January 19, 1911. Dog, weight 10.8 kg. Inflow 80 cm., outflow 60 cm.

	Valve cut.						Valve cut again.						
	1	2	4	5	6	7	A	B	D	F	G	H	I
Plethysmographic swing	17	24	29	25	24	24	25	27	29.5	34	39	33	32
Calibration		1 mm.	= .158 cc.	All res	ults divi	ded by 2.							
Estimate	1.343	1.896	2.291	1.975	1.896	1.896	1.975	2.133	2.33	2.686	3.008	2.607	2.528
Pulse rate	190	160	175	175	175	175	170	165	165	170	160	190	190
No. of beats to give 10 cc	25	16	12.8	17.3	21.5	21.5	8	8.2	7.9	8.2	8.6		
One beat gives	.4	.625	.78	.578	.464	.464	1.25	1.219	1.265	1.219	1.515	1.33	1.33
Residual blood	.943	1.271	1.511	1.397	1.432	1.432	.725	.914	1.065	1.467	1.565	1.277	1.198
Aortic output per minute	76.0	100	134.50	101.15	81.2	81.2	212.5	201.13	208.72	207.2	242.4	252.70	
Heart output (pleth. x rate)	255.1	303	400.9	345.6	331.8	331.8	335.7	351.9	384.4	456.6	492.8	495.3	485.3

In this experiment the inflow pressure was higher than the outflow and was not changed. Insufficiency was slight in the first curve, the parts of which are numbered. In the second curve the heart had gained in vigor and a further tear of the valve was produced between B and D. Apparently the regurgitation was nowhere very great.

TABLE V.—January 11. Dog, weight 11.8 kg. Pressure 60 cm.

	Normal.	Aortic insufficiency.
Pleth. swing	15	25
Calibration	1 mm. = .079	
Estimate	1.185	1.975
Pulse rate	160	130
No. of beats to give 10 cc	19.8	19.7
One beat gives	0.505	0.507
Residual blood	.680	1.468
Heart's work per min. (pleth. x rate)	189.6	256.75

TABLE VI.—March 14, 1911. Weight 6 kg.

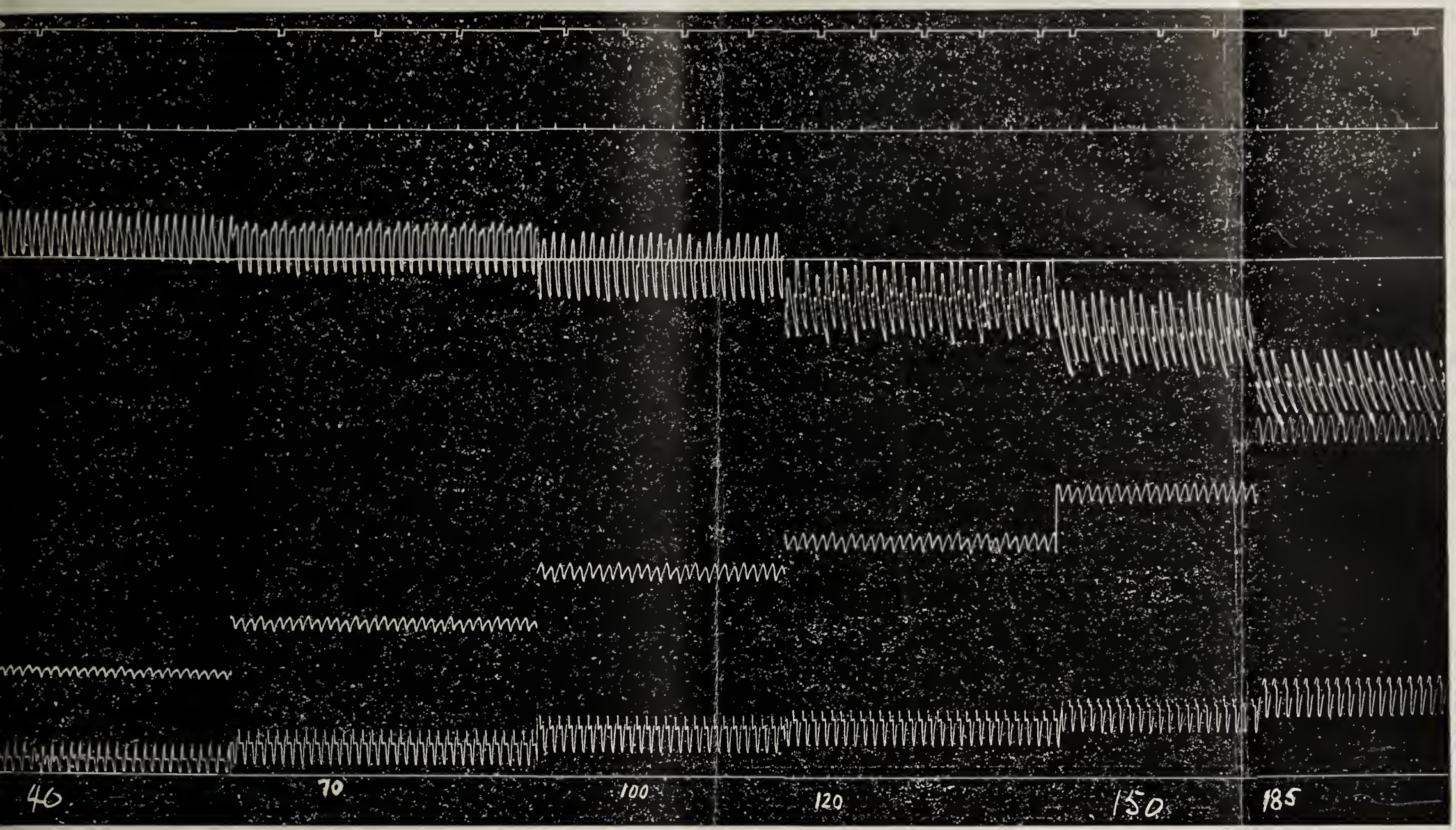
	Normal.		Aortic Insufficiency.				
	A	B	C	D	E	F	G
Periph. pressure	80	120	120	70	40	150	150
Pleth. swing	14.3	18	27.5	16.24	13.26	29.6	37.7
Calibration	1 mm.	=.01584	All re	sults d	ivided	by 2.	
Estimate	1.1297	1.4256	2.178	1.286	1.05	2.344	2.9858
Pulse rate	150	155	160	180	160	160	160
No. of beats to give 10 cc	10	7.6	7	11	16	5.5	5.5
One beat gives	1	1.316	1.4285	0.909	0.625	1.818	1.818
Residual blood	.1297	.1096	.7495	.377	.325	.526	1.1678
Aortic output per min.	150	203	228	163	100	290.8	290.8
Cardiac output per min. (pleth. x rate)	169.4	220.9	348.4	231.48	223	375	477.7

TABLE VII. April 24. Dog, wt. 7.6 kg. Small aperture pierced in valve.

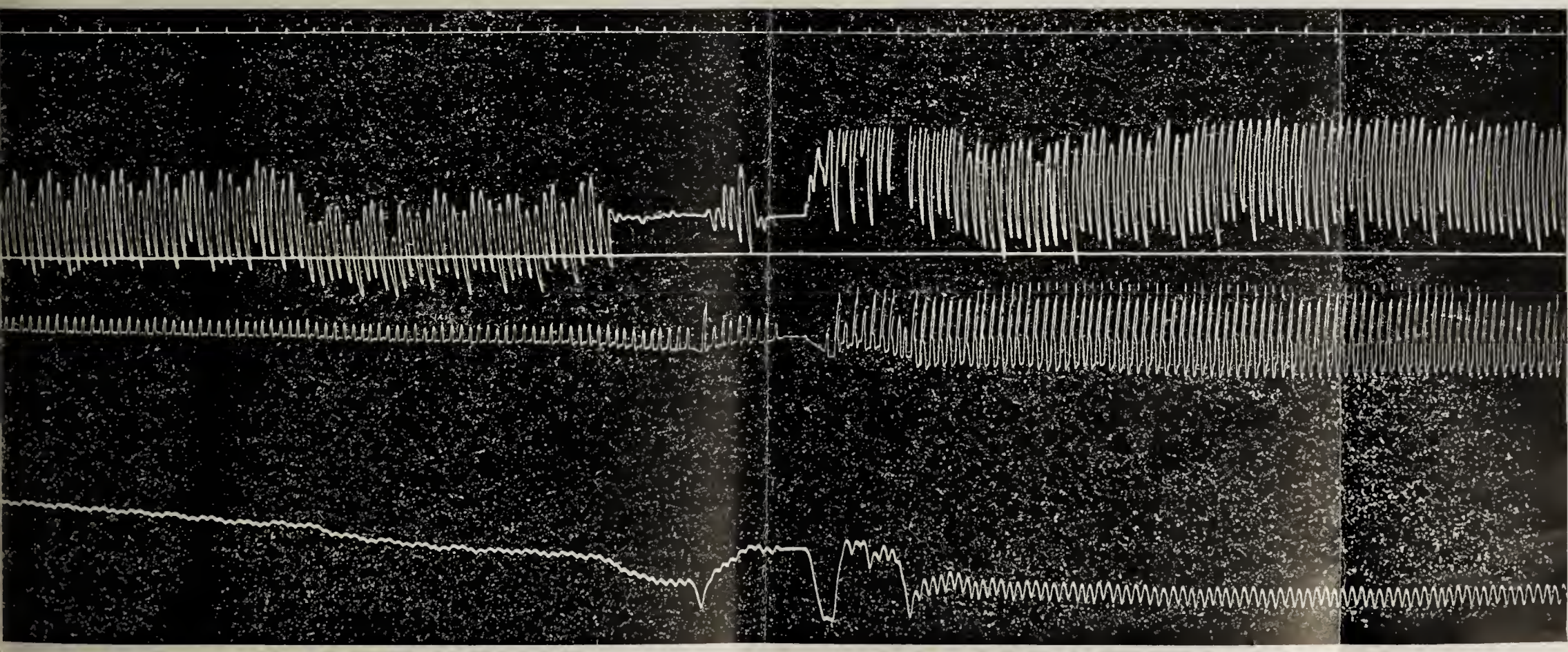
	Valve cut.			
Pressures.	100	120	120	100
Pleth. swing	20.1	27	28.16	24.8
Calibration		5 cc. =	35 mm.	
Estimate	28.7	38.5	40.2	32.57
Pulse rate	200	195	190	195
Number of beats to give 10 cc	7	5.8	5.7	6.5
One beat gives	1.42	1.72	1.75	1.53
Residual blood	1.45	2.13	2.27	1.727
Aortic output per minute.	284	335.4	332.5	298.3
Heart output per minute (pleth. x rate)	574	750.7	763.8	635.1

TABLE VIII. April 24, 1911. Dog, weight 9.4 kg.

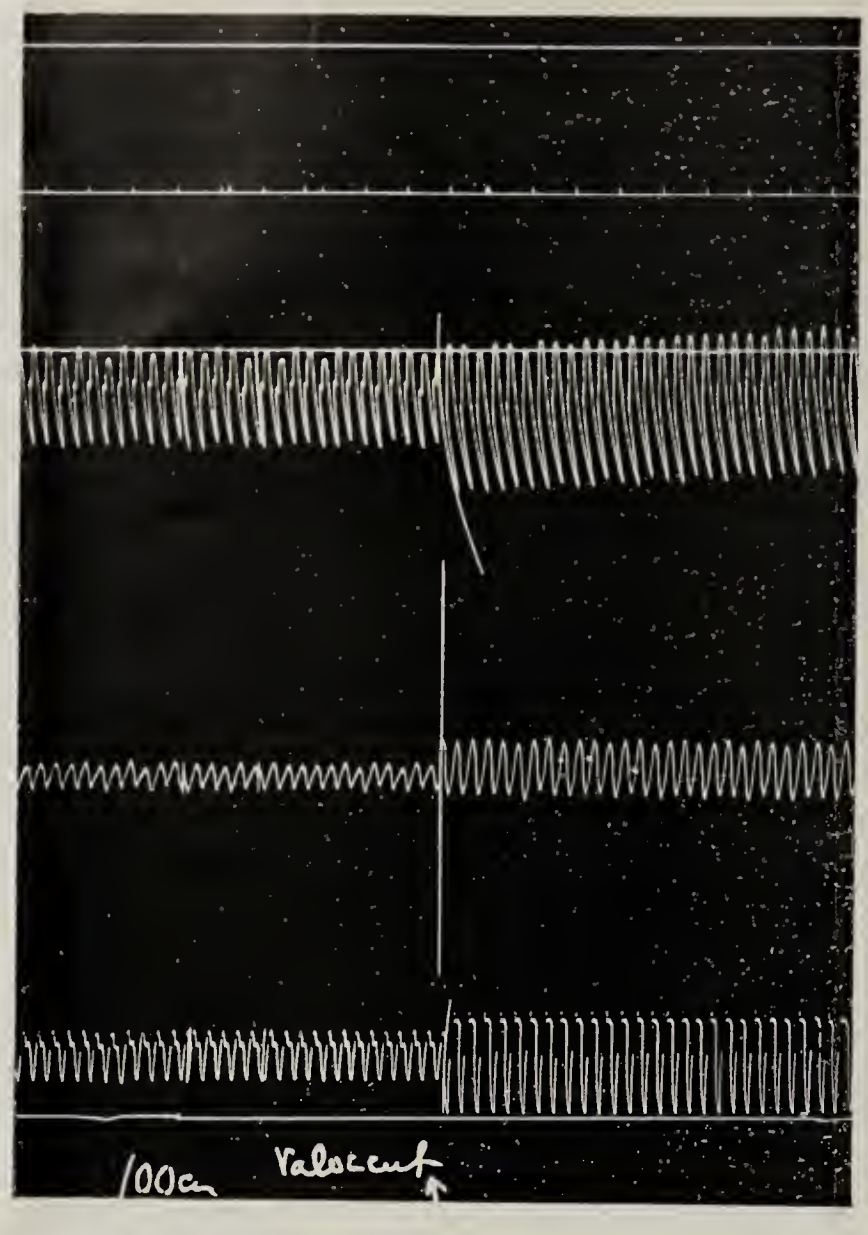
	Aortic valve cut.			
Pressures	100	120	120	100
Pleth. swing	10.3	13.66	20.9 (17.46)	18.2
Calibration		35 mm. =	5 cc.	
Estimate	1.47	1.95	2.98 (2.49)	2.6
Pulse rate	250	250	250	240
Number of beats per 10 cc.	8.26	7.5	7.3 (7.8)	8.57
One beat gives	1.21	1.33	1.37 (1.28)	1.166
Residual blood	0.26	0.62	1.61 (1.21)	1.434
Aortic output per minute.	302.50	332.50	342.50	279.84
Heart output per minute. (pleth. x rate)	367	487.5	745	624



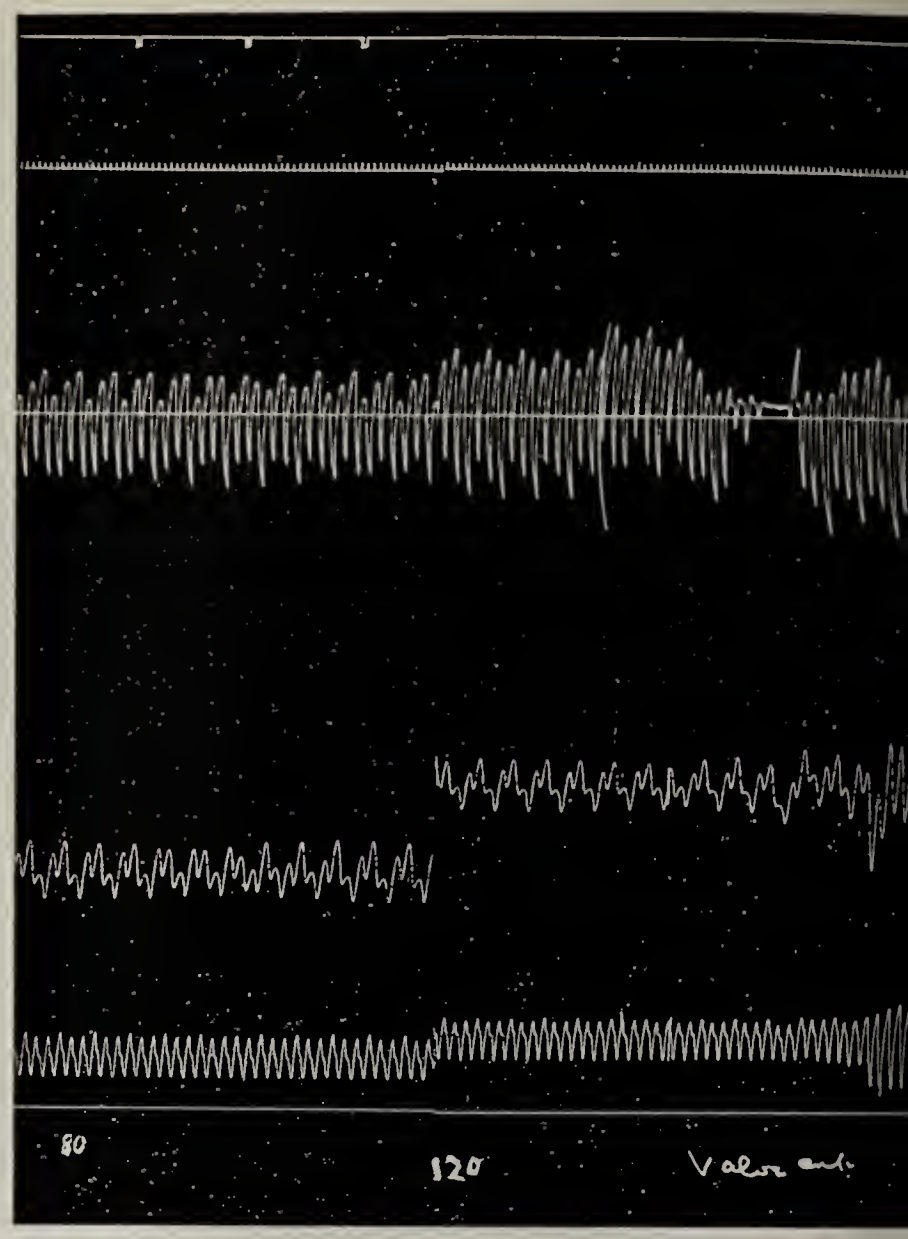
Curve I.—March 30. Dog weight 9 kg. The curve shows the changes in the position of the dicrotic notch, upon the Hürthle tracing and the distension of the heart with increasing inflow of blood. The excursion of the heart is also seen to be greater at the higher pressure.



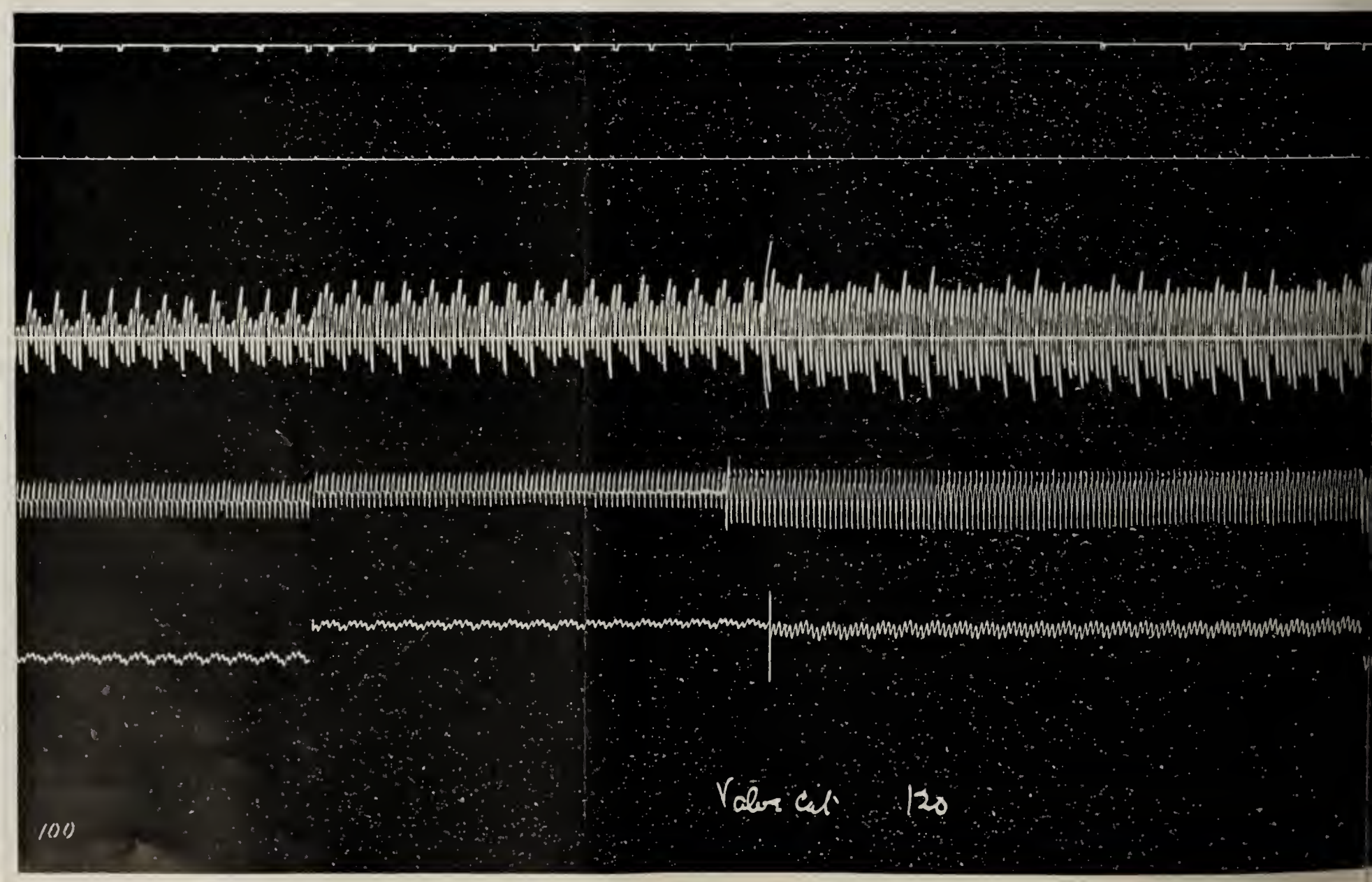
Curve II.—May 7th. Dog weight 7.2 kg. Plethysmographic and other tracings from dog with intact aorta, and after the tearing of the aortic valve. The plethysmographic excursion is increased and the increased pulse pressure is characteristically shown in the curve from the Hürthle manometer.



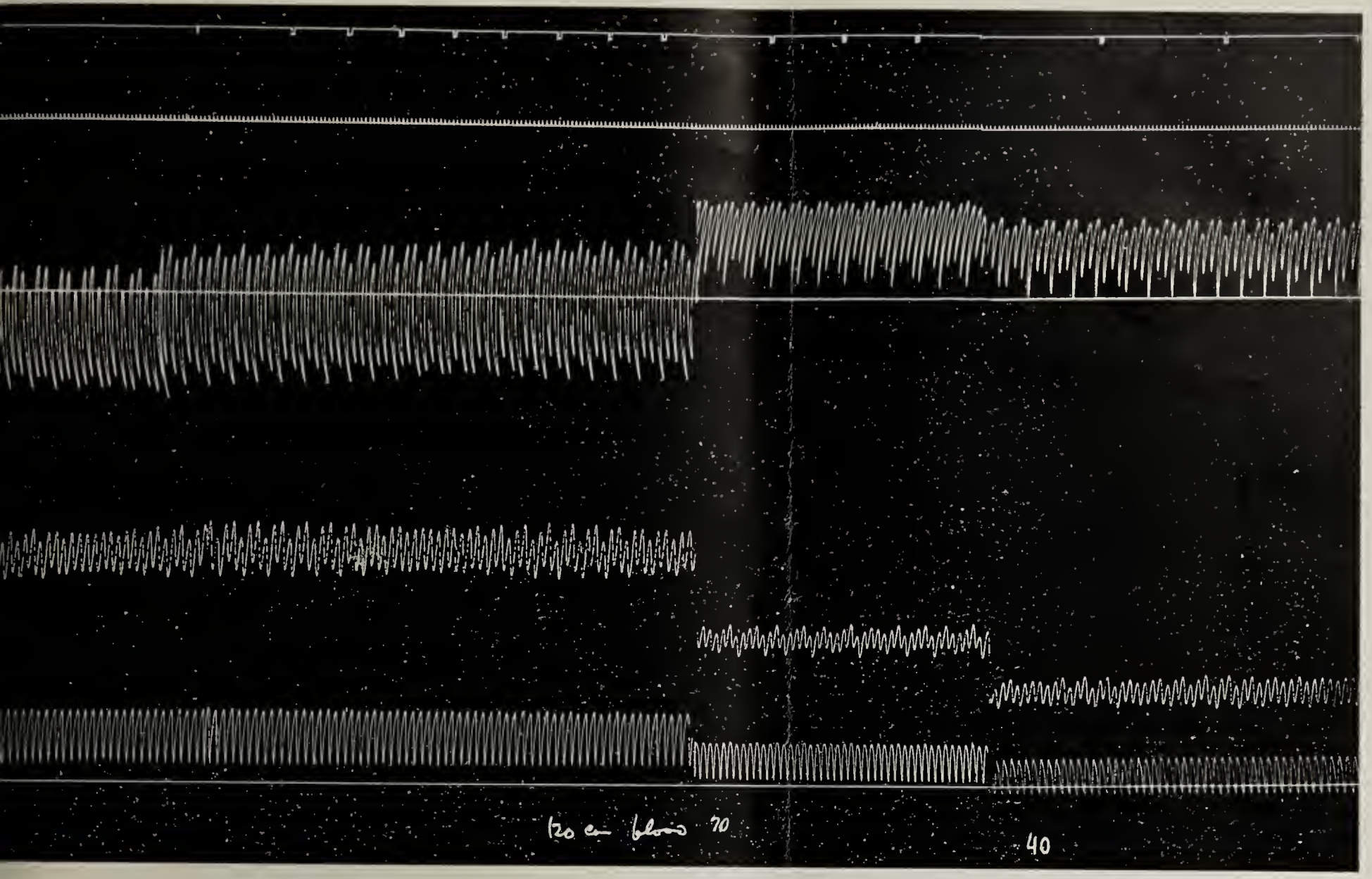
CURVE III.—March 30. Dog weight 9 kg. Characteristic change in all curves on tearing of the aortic valve.



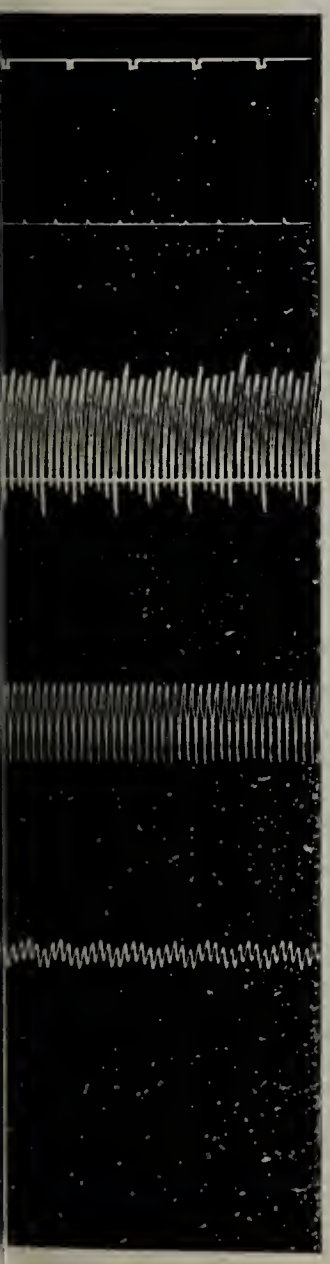
CURVE IV.—March 14. C



CURVE V.—April 24. Dog weight 9.4 kg. Curves at pressures of 100 and 120 cm. of blood, before and after cutting of



outflow and inflow pressures of 80, 120, 70 and 40 cm., before and after cutting of aortic valve.



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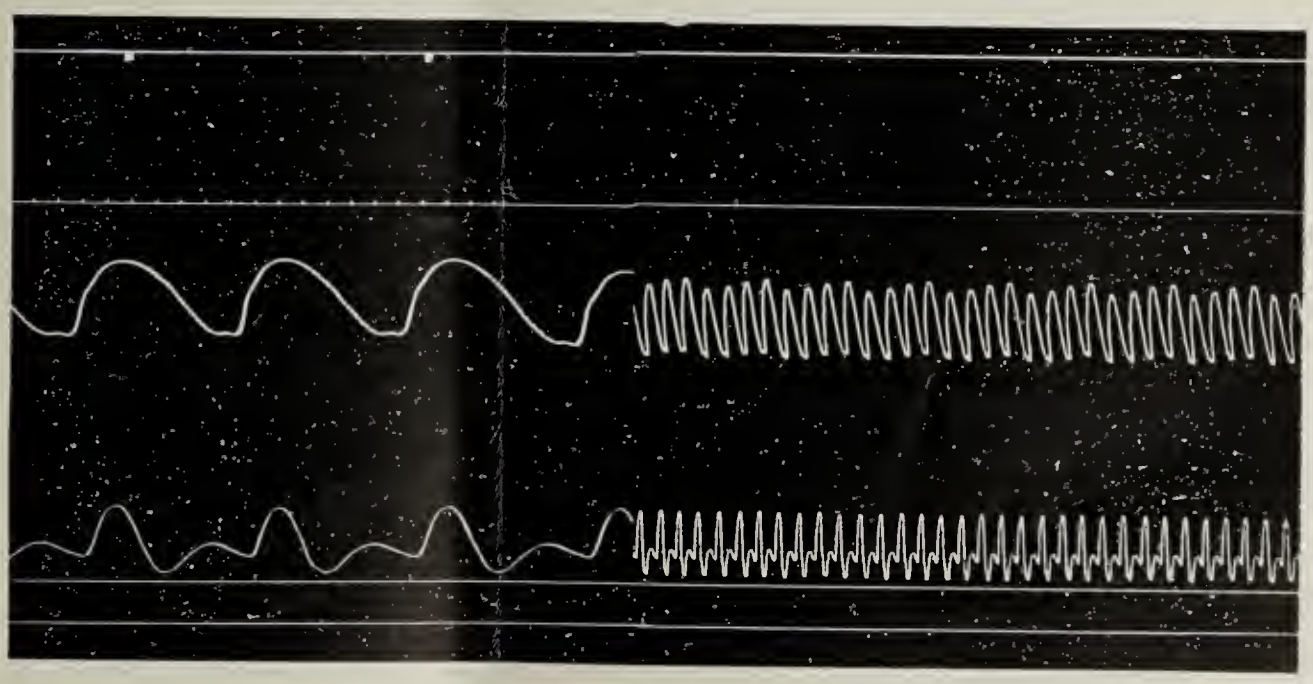
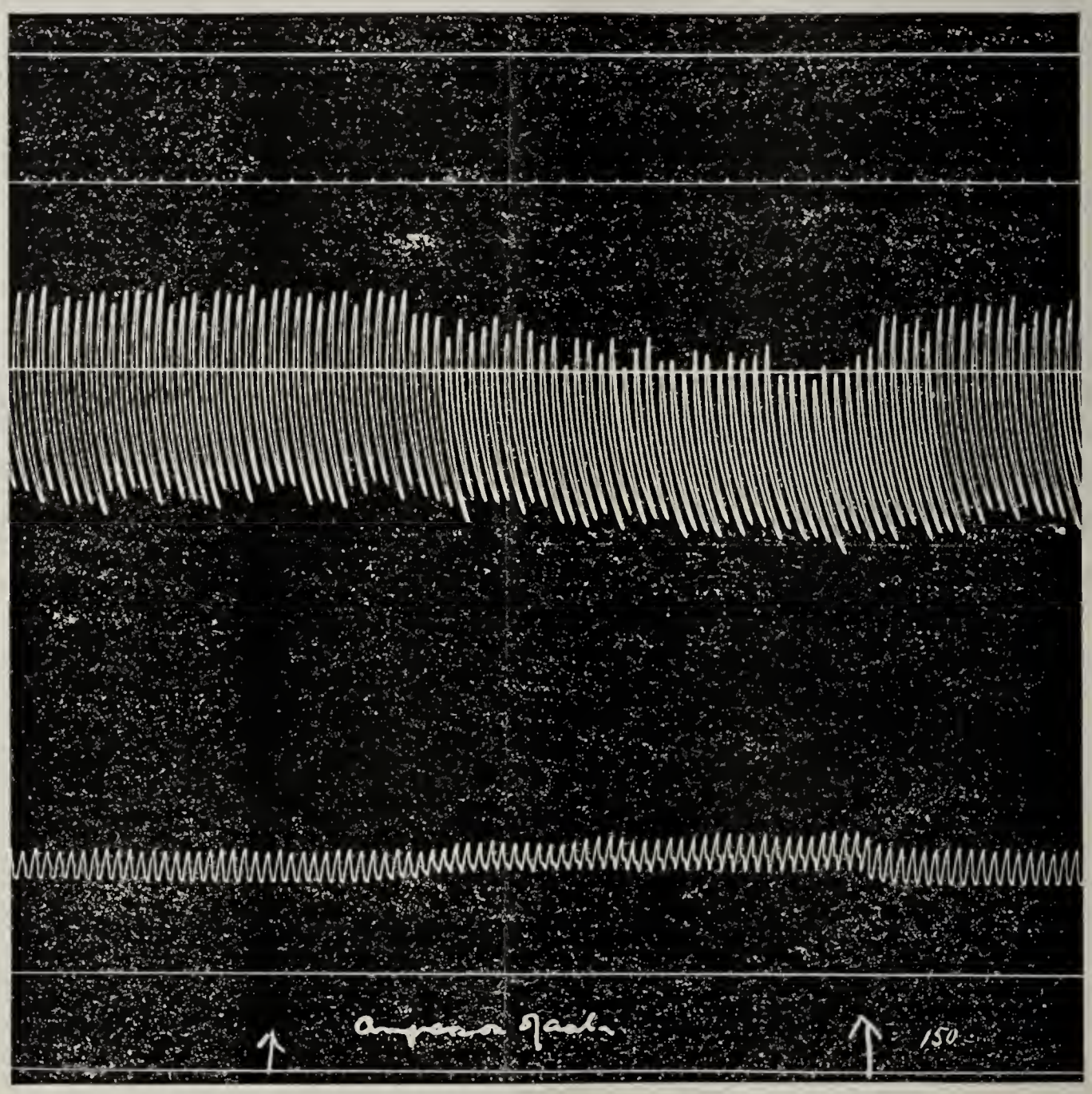
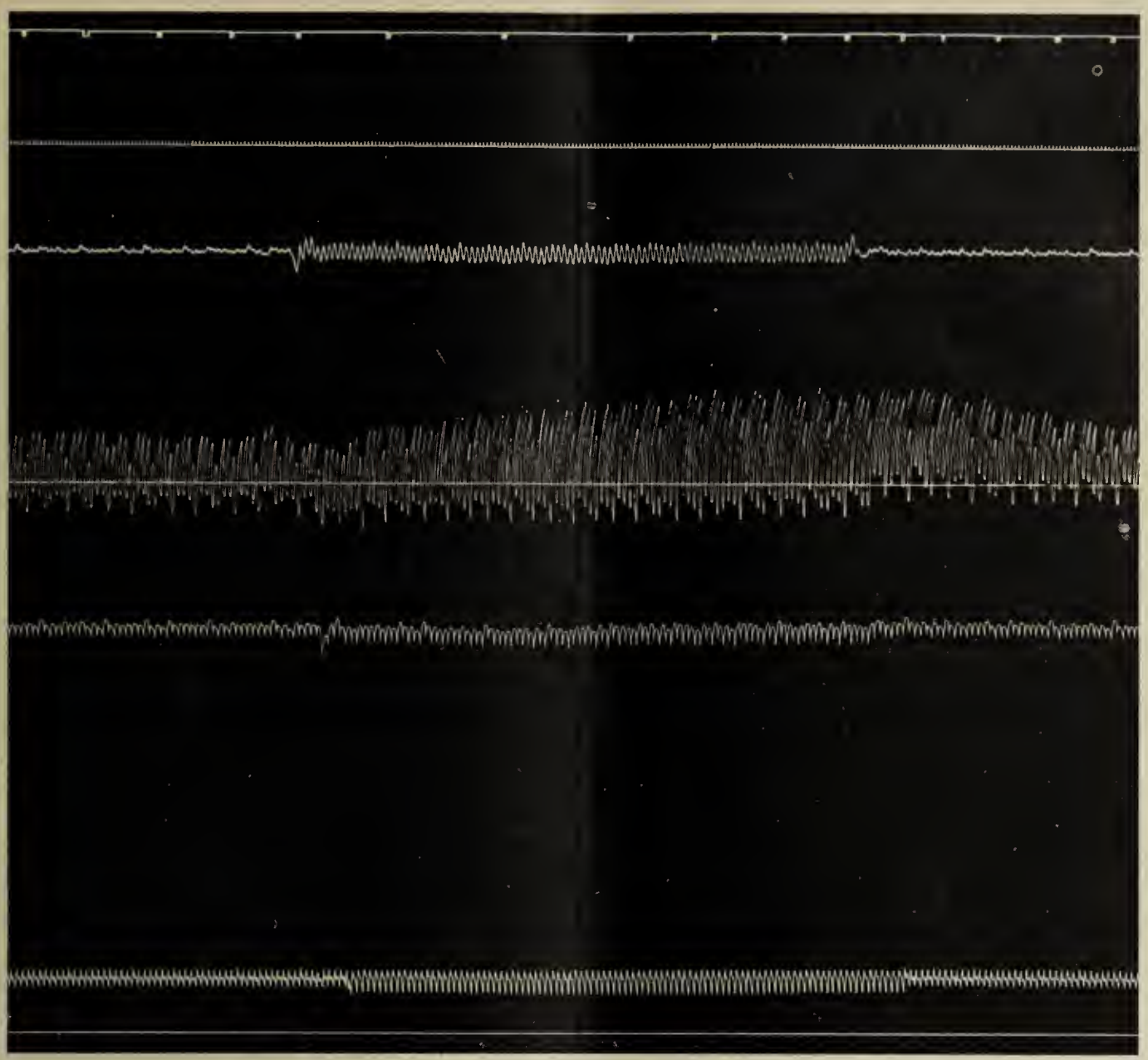


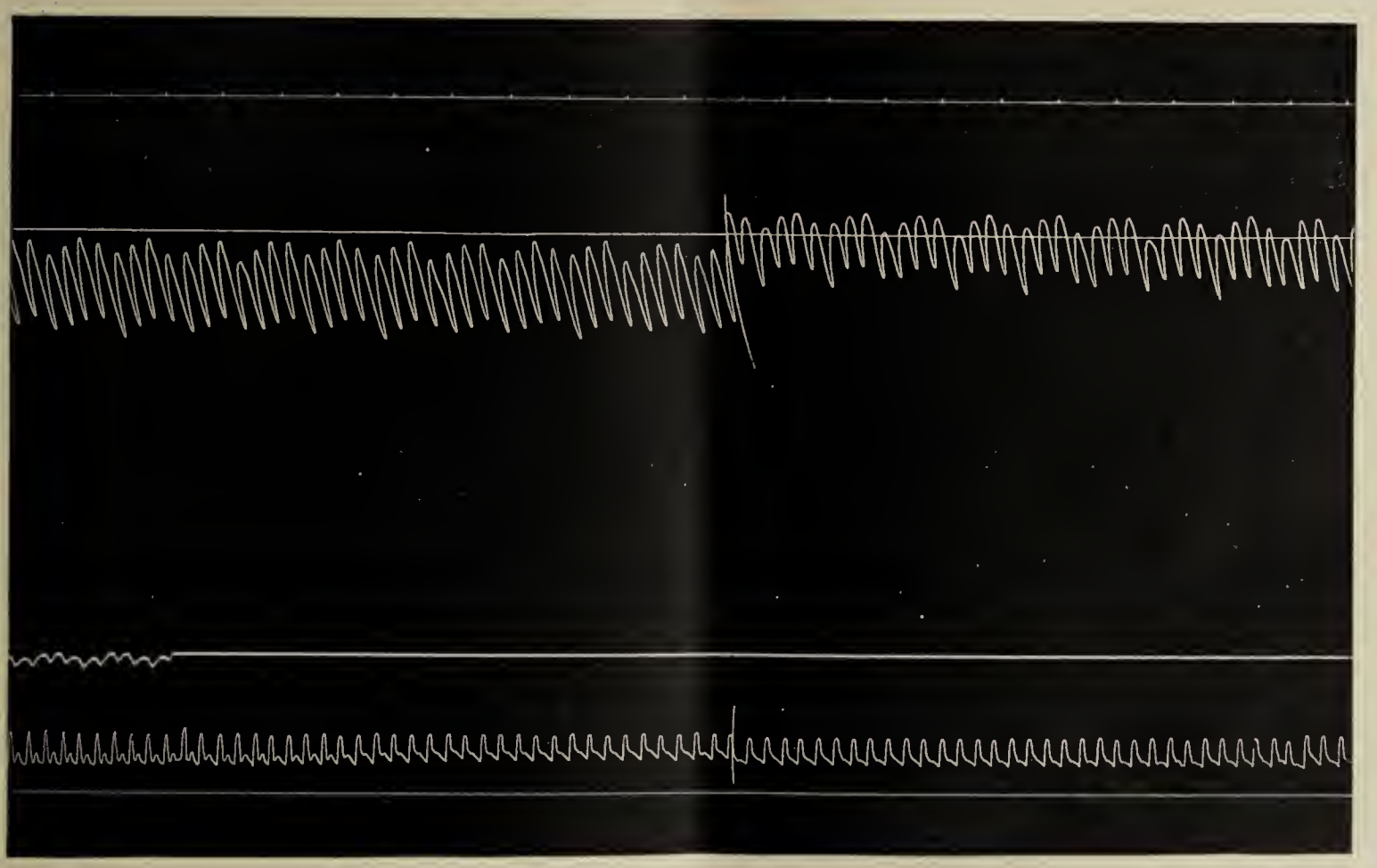
Curve VI.—April 17. Plethysmographic and Hürthle curves in aortic insufficiency in the curve which has become hyperdicrotic. It was in this curve that auscultation showed the part of the curve occupied by the murmur.



CURVE VII.—April 6. Dog weight 6.3 kg. Curve shows the accentuation and elevation on the slope, of the dicrotic notch on compression of the aorta.



CURVE VIII.—February 7. The curve shows the appearance of a collapsing pulse produced by allowing regurgitation from the artificial aorta by tapping it with a "T" tube as described in the text. It is observed that the output is decreased during this regurgitation. Other particulars are mentioned in the text.



CURVE IX.—Shows absence of alteration of character of pulse on introducing artificial arrangement of circulation. It also shows that the fling of the mercury manometer has no influence upon the Hürthle record.

A FURTHER NOTE ON THE CLINICAL USE OF SCARLET RED AND ITS COMPONENT AMIDOAZOTOLUOL, IN STIMULATING THE EPITHELIATION OF GRANULATING SURFACES.*

By John Staige Davis, M. D.,

Instructor in Surgery, The Johns Hopkins University.

Introduction.—In a paper published in The Johns Hopkins Hospital Bulletin, in June, 1909, I reported the results of my observations during the treatment of 60 cases with scarlet red in various combinations.

Since that time I have been impressed by the great interest in the clinical use of this dyestuff as shown by the large number of papers on this subject which have appeared in the foreign journals, and also by a number of personal communications reporting favorable results.

The object of this article is to bring the subject up to date as far as possible, and in addition to make a few observations on the clinical use of amidoazotoluol, which was first tried by Hayward† and is a component of the scarlet red originally used by Fischer.

I was very skeptical when I began to experiment with scarlet red. It was difficult to believe that by the application of a commercial dyestuff such rapid epithelial stimulation could take place in sluggish wounds, some of which had been unhealed for many years.

It has been suggested that possibly the wounds healed with scarlet red were in a period of development in which, after being inactive for a longer or shorter time, the rapid epithelial growth would have taken place just as well under any other method of dressing. This may be true in a few instances, but I hardly believe it could have been the case in the large number of cases reported, where the process of healing had been at a standstill until this dressing was begun.

Carrel, in his very interesting article on "The Treatment of Wounds" (J. Am. M. Ass., 1910, p. 2148), says that when at the end of the period of "granulous retraction" of a large wound the edges of the old epidermis are still at a distance of 20-25 mm., the new epidermis cannot spread on the granulations and the cicatrization of the wound comes to a standstill.

Now, in practically all of the wounds which I have treated with scarlet red and amidoazotoluol, the period of "granulous retraction" had long since ceased, the period of epidermization had also come to a standstill, and the areas were, for the most part, very large. In spite of these facts, in the large majority of cases there was marked epithelial stimulation from the hitherto sluggish edges following the application of the dyestuff, and subsequent rapid healing.

Scarlet red was used exclusively as a dye until 1900, when Michaelis found that this coloring matter was very suitable for staining fat in the cellular tissue for microscopic examination.

Experimental Use.—B. Fischer in 1906, in a paper on the "Experimental Generation of Atypical Epithelial Proliferation," produced by the subcutaneous injection of a saturated solution of scarlet red, in olive oil, in a rabbit's ear, first called attention to the remarkable stimulating properties of this dyestuff, and suggested that therapeutic advantage might be taken of it. Since his publication a number of investigators (Ritter, Jores, Geipel, Snow, Stahr, Wyss, Helmholz, McConnell, Seekel, Hertzler, Schreiber and Wengler, Werner, Enroth, Stoeber, Grimani, Dixon, Cords, Wessley, Meyer, Borst), following Fischer's lead, have repeated his experiments and extended them. As far as I can ascertain, all, with the exception of Snow, have agreed that a new growth of epithelium is produced.

Several kinds of animals have been used, rabbits, Belgian hares, guinea pigs, white rats, mice, monkeys, dogs, cats, etc. These proliferations have also been produced in man. Wessley experimented on himself, and Stoeber upon a man 80 years old, whose leg was to be amputated for ununited fracture. The results were not as marked as in the rabbit's ear, on account of anatomical conditions, but were definitely positive. Stoeber injected scarlet red, amidoazotoluol and alpha naphthylamin, but did not succeed in producing epithelial proliferation by alpha naphthylamin. It is beyond the scope of this paper to discuss the theories as to the cause and source of these atypical epithelial proliferations.

An interesting point is made by Claribel Cone, who says that in the epidermis of man the fat which is shown by the scarlet red stain is especially noted in the basal (germinal) layer at the point of contact of the cell body and nucleus; in other words that the scarlet red attacks the living cell just at the point where physiological cell changes are most active. She suggests that this may cause a chemical or physical stimulation of the cell, and thus account for the active proliferation following its clinical use.

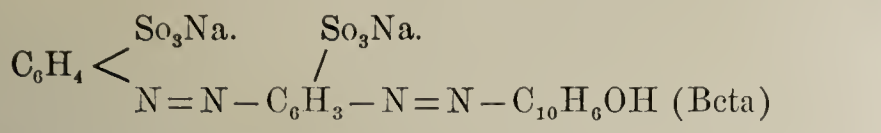
Chemistry.—In looking over the literature on the clinical and experimental use of scarlet red I find that there are several chemically different dyestuffs which are marketed under the name scarlet red. I will consider the chemical formulæ of four of these.

(1) The dye used in my series in 1909 was the sodium salt of diazo-azo-benzene-disulphonic acid Beta naphthol.

Commercial Names.—Biebrich Scarlet; Pouceau 3 RB; Pouceau B; Fast Pouceau B; New Red L; Imperial Scarlet (Schultz & Julius, 1904, p. 110, No. 163).

* Read before the Johns Hopkins Hospital Medical Society, April 3, 1911.

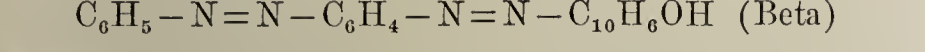
† All references are arranged alphabetically under "Bibliography" at end of this article, so that the papers referred to under authors' names are readily to be found.



Method of Preparation.—Amido-azo-benzene-disulphonic acid and Beta naphthol. It is a red powder, soluble in water and slightly soluble in alcohol. Insoluble in ether.

(2) Benzene-azo-benzene-azo Beta naphthol.

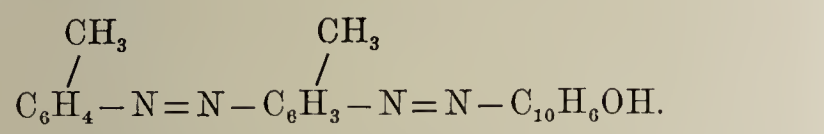
Commercial Names.—Soudan III; Cerasine Red (Schultz & Julius, 1904, p. 106, No. 143).



Method of Preparation.—Amido-azo-benzene and Beta naphthol. It is a brown powder, soluble in alcohol and fats. Insoluble in water.

(3) Toluene-azotoluene-azo Beta naphthol. This is the scarlet red originally used by Fischer and Schmieden.

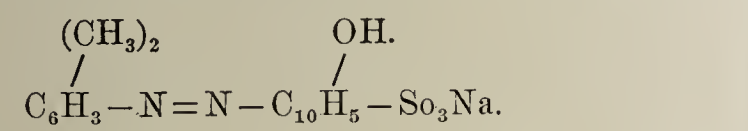
Commercial Names.—Oil Scarlet; Red B Oil Soluble Extra-concentrated; Pouceau 3 B (Schultz & Julius, 1904, p. 108, No. 150).



Method of Preparation.—Amido-azo-ortho-toluene and Beta naphthol. It is a dark reddish-brown powder which cakes at about 175° C. and melts at 184° to 186° C. Insoluble in water, soluble in alcohol and chloroform, fats, fatty oils, and also warmed vaseline and paraffine.

(4) Sodium salt of xylene-azo Beta naphthol monosulphonic acid.

Commercial Names.—Scarlet G. R; Scarlet R; Brilliant Orange R; Orange L (Schultz & Julius, 1904, p. 86, No. 54).

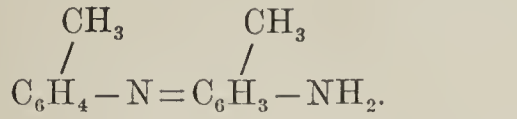


Method of Preparation.—Xylidene and Beta naphthol monosulphonic acid. It is a cinnibar red powder, soluble in water.

I have used clinically the first three of these preparations with success, and also xylidene scarlet (Schultz & Julius, 1904, p. 96, No. 55) which is closely related to the fourth preparation. I find the best and most consistent results with scarlet red have followed the use of the dyestuff originally employed by Fischer and Schmieden. Hayward says that in the few cases reported where no result was attained this special dye was probably not used. He has also experimented with Soudan I, Soudan IV and Soudan G, with more or less success.

He says that Fischer and Schmieden thought that Alpha naphthylamin caused the epithelial stimulation in the most far-reaching way. Hayward used this substance clinically, and found that it caused only marked irritation. This was also my experience when I used Beta naphthol ointment of a strength corresponding to that actually entering into the formation of 8 per cent scarlet red, i. e., 2.4 per cent.

Experimenting further Hayward employed amidoazotoluol, the other component of scarlet red, and found that this substance caused a more marked stimulating effect on the growth of epithelium than did the scarlet red.



Method of Preparation.—Slowly add a saturated solution of sodium nitrate (1 mol.) to a mixture of orthotoluidine (4 mols.) and concentrated hyrochloric acid (2 mols.) and keep at a temperature of 30° to 40°. It is a reddish-brown granular powder. Melting point about 100° C. Nearly insoluble in water, but easily soluble in alcohol and ether.

CLINICAL USE.—A few words concerning the papers which have appeared on the clinical use of these substances may be of interest.

Schmieden was the first to follow Fischer's suggestion that scarlet red be used therapeutically, and in February, 1908, published a paper on his clinical results, which were very favorable. He reported rapid healing of sluggish ulcers of various kinds and in different situations. He used 8 per cent ointment and alternated the dressing every 24 hours with some bland ointment on account of the irritating properties of the scarlet red. He also used with success adhesive plaster impregnated with 10 per cent scarlet red for strapping leg ulcers.

He insisted that the granulations must be perfectly clean and flat, and said that it was useless to apply the ointment to an unclean ulcer. He noted that there was little chance of cicatricial contraction under this healing, and showed by microscopic examination that the newly formed skin was the same as the normal skin.

In May, 1908, Kaehler substantiated Schmieden's work and modified his technic. He found good results could also be obtained when scarlet red was used on unhealthy granulating wounds. He healed a varicose ulcer with scarlet red, and then was able to thoroughly clean up this new skin and operate through it for excision of varicose veins, thus showing the stability and quality of the newly formed epithelium. He completely healed defects of similar size, one with grafts and one with scarlet red, in exactly the same time.

Krajca, in September, 1908, described further good results. He was the first to use scarlet red in conjunction with partial Thiersch grafts, and found that the edges of the grafts were stimulated as well as the wound edges. He mentions a number of interesting cases. Some of the ulcers, although of large size, healed in a very short time under this treatment. He found the cutaneous irritation due to the scarlet red to be the exception rather than the rule.

Enderlen, in September, 1908, published very satisfactory results, as did Cernezzi and Hubner, in February, 1909. Wolfrom and Cords in the same month wrote on the successful treatment of ulcers and wounds of the cornea by 5 per cent scarlet red salve. Excellent results were obtained in a case of keratitis neuroparalytica. An old corneal fistula was closed by this means. A more rapid regeneration of the tissues was

noted and sometimes an excess of tissue formation, but this soon flattened.

Sprecher, in March, 1909, reported good results in the treatment of ulcerated lupus vulgaris, ulcers of prepuce, vulva, labia and cervix, varicose leg ulcers, syphilitic ulcers, ulcers of the breast, etc. He did not observe any local irritation or toxic effect in his series.

Rebaudi, in April, 1909, described the use of scarlet red in gynecological conditions and obtained excellent results in the treatment of erosions, tears, etc.

Pleth and Pleth, in May, 1909, detailed the successful use of scarlet red on ulcers of various kinds. Heermann, in June, 1909, reported the success of his treatment with scarlet red of tympanic membrane perforations. He said the duration of the perforation seemingly had no effect on the rapidity of the healing. Suppuration did not appear during this treatment.

Ducros, in July, 1909, reported favorable results on granulating wounds, as did Morawetz, in September of the same year. Hayward wrote in the same month concerning the use of an 8 per cent ointment of amidoazotoluol, which is, as I have mentioned before, a component of the scarlet red used by Fischer. His results on a number of granulating wounds were even more favorable than with the scarlet red, and he felt convinced that this was the stimulating portion of the dyestuff.

It does not seem possible that amidoazotoluol is alone responsible for the epithelial stimulation, as a number of observers, myself included, have noted very favorable results produced by the clinical used of dyestuffs which do not contain amidoazotoluol.

Grossmann, in December, 1909, reported favorable results with scarlet red salve, amidoazotoluol ointment and amidoazotoluol gauze, in the treatment of wounds following operations on the nasal passages, and in perforated tympanic membranes. Halle, and also Levy, said that they had been successful in similar cases with the scarlet red.

Hartman and Beyer stated at the same meeting that they had used scarlet red in a small number of cases without any particular success. Sonntag and Brühl said they had failed to get rapid results in similar cases.

Auerbach, in 1909, published a number of successful results in the treatment of ulcers occurring in skin and venereal diseases, varicose ulcers, etc. He was unsuccessful in only one case, a multiple leg ulcer which was complicated by extensive varices. The other leg of this patient had been previously amputated for leg ulcer. He used the treatment with success on wounds which were discharging copious purulent secretions. He had irritation with 8 per cent scarlet red, so tried 4 per cent, which he found could be used continuously. Dauthuile also reported favorable results.

The papers which have appeared in 1910 are as follows: Rammstedt and Jacobsthal mentioned excellent results in the healing of ulcers due to X-ray burns. Dreifuss reported favorable results in the treatment of granulating wounds. Cords said it was of use in the eye only in clean ulcers of the cornea, especially if there was deep loss of substance.

Pein detailed a number of cases successfully treated with scarlet red, and gave a very interesting table of the measurements, taken from 25 leg ulcers, from the beginning of the treatment to the time of healing.

Strauss published his very favorable results in the treatment of X-ray burns and other ulcers of various kinds. He says he does not value the use of scarlet red for the rapidity of epitheliation alone, which, in some cases, does away with the necessity of Thiersch grafting, but for the solid epithelium which is of great value, especially in the region of the joints. By this healing contractions and scar tensions can be avoided. Stein reported good results in otiatrics. Scharezki was very successful in the treatment of skin defects of various kinds.

Katz reported favorable results with 8 per cent scarlet red and amidoazotoluol. Simin had excellent results following the use of scarlet red.

Nance (J. Ophth., Otol. & Laryngol., 1911, p. 41) reported very favorable results with scarlet red in the treatment of corneal defects.

It can be seen from the above that by the use of scarlet red and amidoazotoluol very satisfactory results have been obtained. The tone of nearly all of these papers has been enthusiastic, and the only unfavorable results are those reported by Hartmann and Beyer, Sonntag and Brühl. All of these were in aural cases.

Since the publication of my paper I have continued to use scarlet red on a number of other cases with almost uniform success, and have little to add to the technic described at that time.

I find marked epithelial stimulation even when the wounds are unhealthy and the discharge is profuse. This has also been the experience of Kaehler and Auerbach, although nearly all the other writers, beginning with Schmieden, have stated that it is useless to apply the scarlet red ointment to any but a perfectly clean granulating wound. Of course the most rapid results are obtained on flat healthy granulating surfaces, but a great deal of progress can be made by its use while the granulations are being brought into this condition.

Strauss objects to the use of scarlet red put up in balsam of Peru ointment, blue ointment, iodoform ointment, etc., as recommended by me, in the treatment of unhealthy granulating wounds, on the ground that the ointment is of no use on such ulcers, but my experience has evidently been very different from his. I consider the use of such combinations to be of value in the treatment of unhealthy granulating wounds, as the scarlet red in itself has no antiseptic qualities, and the cleansing process due to the balsam of Peru, etc., can in this way be carried on while the scarlet red is being used, as well as by the alternating dressing.

Technic.—An outline of the technic will suffice. Cleanse the wound thoroughly with boric or salt solution and dry. Peroxide of hydrogen may be used before the boric solution if the granulations are unhealthy. The free use of a nitrate of

silver stick is advised to keep down exuberant granulations. Tincture of iodine, U. S. P. strength, may follow the silver nitrate or be used on alternating days, and is a powerful and rapid method of cleansing granulations.

The strength of the scarlet red ointment ordinarily used is 8 per cent, and it should be alternated every 24 to 48 hours with some bland ointment. By applying a weaker ointment, say 4 per cent, it can be used over longer periods without danger of the severe irritation which occasionally occurs.

The most satisfactory method of applying the ointment is as follows: Anoint the skin surrounding the defect with some bland ointment up to about one centimeter of the wound edge, as this prevents possible irritation. Then spread the scarlet red ointment in a thin layer on perforated old linen and apply to the wound, either along the edges or over the whole surface. A light dressing of sterile gauze secured by a bandage completes the procedure.

I have applied the scarlet red ointment to a number of wounds and then exposed them to the air and sunlight. The healing is very rapid and the drying out of the surface is most noticeable.

It is safe to use a 4 per cent scarlet red ointment on partial skin grafts of all kinds 48 hours after grafting, and there is rapid stimulation of the wound edges and also of the grafts themselves.

Case Reports.—I will mention only one case to illustrate the efficacy of scarlet red. A very feeble old lady, 84 years old, was badly burned across the shoulders six weeks before she came under my care. During that time she had been carefully treated by her family physician with the usual methods. The wounds had done well for several weeks, and then had become sluggish and no further progress could be made. The patient's general condition was bad on account of a weak heart and chronic nephritis, and was becoming serious under the strain. I was called to consider the advisability of grafting.

There were three ulcers, one over the right scapula, 5 x 10 cm., another over the left scapula, 5 x 8 cm., and a third ulcer 8 x 10 cm. situated in the mid-line between the other two. Those over the scapulæ were covered with clean, but edematous granulations, which had not yet reached the level of the skin. The central wound was still covered, to a large extent, by a slough which was made up of the whole thickness of the skin and some subcutaneous tissue. The epithelial edges of these ulcers were very sluggish.

On account of the condition of the patient and the situation of the wounds, I decided to try scarlet red instead of grafting.

November 26-27, 1910. The wounds were dressed with a balsam of Peru and castor oil mixture, 1 to 3.

November 28. Scarlet red, 8 per cent, was applied, and thereafter every third day, alternating with boric ointment.

December 7. The last of the slough was removed.

December 16. The wound over the left scapula was healed.

December 23. The central wound was healed.

December 25. The wound over the right scapula was healed.

During the treatment the patient was in a critical condition almost continuously and had to be strongly stimulated in order to preserve her life.

The case is instructive from the fact that old age and great debility seem to have little deterrent effect on the stimulating power of scarlet red. The skin edges were stimulated in spite of the presence of a slough in the central wound. It was only necessary to use the scarlet red ointment in nine dressings to complete the healing. The result was a firm, thick and stable skin, which showed no tendency to contract.

After the appearance of Hayward's paper on the efficacy of amidoazotoluol, I had the opportunity of using this substance on a number of granulating wounds of varying etiology. The results have been excellent.

Calculating the amount of amidoazotoluol in scarlet red from the molecular weights, we find that there is 3.76 per

Fig. 1a.

cent of amidoazotoluol in an 8 per cent scarlet red ointment. I have used this strength as well as 8 per cent in simple vaseline, and also in the balsam of Peru and other ointments suggested earlier in the paper. I will illustrate the efficacy of amidoazotoluol by briefly reporting two cases.

Case I.—A boy, 14 years old, fell into the fire while in an epileptic attack and was severely burned. He was admitted to the hospital and was much improved, during his five months' stay, by grafting and various other methods. He was then sent to the Out-Patient Department for dressing, and as no further progress was made in the healing he was referred to me eight months after the accident.

The size of the unhealed areas at this time can be well made out in the illustrations. The wounds were covered with very exuberant granulations which secreted actively. The epithelial edges were at a standstill. The patient refused to be grafted and it was decided to try eight per cent amidoazotoluol ointment. The granulations were trimmed off with scissors, then cauterized with silver nitrate, and this was followed by tincture of iodin. This

procedure was carried out whenever necessary throughout the treatment.

February 24, 1910 (Fig. 1, a and b). All of the ulcers were dressed with amidoazotoluol ointment and this was alternated every 24 to 48 hours with balsam of Peru and oil, zinc oxide or

FIG. 1B.

FIG. 1C.

FIG. 1.—CASE I. Sluggish ulcers following burn. Healed with amidoazotoluol. a, b, taken February 24, 1910, eight months after the accident. The ulcers are surrounded by scar tissue. There is partial web formation in the axilla. The exuberant granulations and sluggish wound edges can be well seen. c, taken May 9, 1910. Shows the character of the healing. There is no tendency to contraction. The web formation is less marked.

boric ointment. A stimulation of the epithelial edges was noticeable within 48 hours.

After the first dressing of the large areas with amidoazotoluol a temporary change of color was noticed in the urine. The patient was dressed at 5 p. m. and the urine voided was as follows: February 24, 6.40 p. m. watery, 500 cc., 9.30 p. m. light lemon, 450 cc.; February 25, 4.30 a. m. *amber*, 430 cc., 7.50 a. m. *reddish brown*, 240 cc., 11 a. m. *reddish brown, slightly darker*, 80 cc., 2.30 p. m. watery, 280 cc., 5.55 p. m. watery, 200 cc., 7.00 p. m. watery, 360 cc. Otherwise the urine was negative. The subsequent dressings did not cause a change in the color of the urine.

May 9. The patient was discharged entirely healed (Fig. 1, c). The healing was firm, thick, and looked like normal skin. Examination of this patient 6 months later showed a firm, movable skin, with normal sensation and no tendency to contraction.

CASE II.—A man, 30 years old, was severly burned by an explosion of oil. He came under my care on May 5, six months after the accident, and one of the unhealed areas is well shown in the figure. This wound had improved for a time and then had become sluggish and apparently no further progress could be made from the epithelial edges. Several unsuccessful graftings had been previously done.

The wound was covered with edematous exuberant granulations which were exquisitely tender. An effort was made to put the granulations in a healthy conditon as soon as possible. Toward the end of this process four per cent amidoazotoluol ointment was

A. B.

FIG. 2.—CASE II. Sluggish ulcer following burn. Healed with small deep grafts and amidoazotoluol. a, taken May 30, 1910, six months after the accident. The ulcer is surrounded by scar tissue. The small deep grafts applied May 28 have all taken and the wound edges have begun to spread. b, taken June 4, 1910. Shows the very rapid epithelial stimulation from the grafts and wound edges after two dressings with amidoazotoluol. The entire wound is healed with the exception of a few small areas, whose aggregate size is not larger than a ten cent piece.

used as a dressing and was followed by marked stimulation of the edges.

On account of the tenderness it was decided to graft. The patient refused to allow Thiersch or whole thickness grafts to be cut.

May 28. The granulations being in good condition a number of small deep grafts were taken from the thigh under local anesthesia, and transplanted on the undisturbed granulations. The grafts were dressed with narrow overlapping strips of protective, over which was placed a dry dressing.

May 30. The dressing was changed, and all the grafts were found to have taken (Fig. 2, a).

June 1. The grafts were dressed with four per cent amidoazotoluol on old linen. When the dressing was removed 48 hours later it was noted that the grafts were markedly stimulated. Dressed with boric ointment.

June 4. The entire wound, with the exception of one or two small areas was covered with epithelium (Fig. 2, b).

June 11. The wound was entirely healed with firm resistant epithelium, which required no further dressing. Four applications of amidoazotoluol had been made. The grafts themselves had become much thickened and projected above the surrounding skin like little warts (Fig. 3, a). This condition disappeared and the entire area assumed the normal level (Fig. 3, b).

Examination of this patient eight months later showed a firm, movable skin with normal sensation. There was still some pigmentation around the grafts, but this was less marked than at date of discharge.

Comments.—I was able to compare the rapidity of healing caused by scarlet red and amidoazotoluol. Following an extensive burn there were two granulating wounds of about the same size. One was dressed with 8 per cent scarlet red ointment and the other with 8 per cent amidoazotoluol ointment. The healing in both was rapid, but the wound dressed with amidoazotoluol healed first. The character of the healing was practically the same.

A. B.

Fig. 3.—Case II. a, taken June 24, 1910. Shows the remarkable thickening of the grafts, which project like little warts above the skin level. b, taken August 9, 1910. The grafts have assumed the level of the surrounding skin. Considerable pigmentation can be seen in the healed area surrounding the grafts.

The age of the patient seems to have little effect on the stimulating power of these ointments. The general health of the patient is most important and in some instances forced feeding, fresh air and tonics must be resorted to.

It is interesting that a number of patients with exquisitely painful ulcers have remarked that there is less discomfort after dressing with these substances that after any other dressing, however bland.

In none of the cases have I noted the slightest irritation of the surrounding skin following the use of amidoazotoluol. Although this dressing can be used continuously without irritation, it is best to apply it for 48 hours and then alternate with some bland ointment for 24 hours.

Dressing with both substances causes excess of secretion for one or two applications, but there is marked drying up of the granulations in a short time.

The use of scarlet red and amidoazotoluol in blue ointment is advantageous in the treatment of syphilitic ulcers, and in addition constitutional treatment should always be employed. In the treatment of second degree burns the ointment can be used immediately after the blisters have been cut away. In third degree burns it is best to wait until the granulations have started.

For a time after healing the newly formed skin has a tendency to be dry and somewhat scaly, but this is easily overcome by the applicaton of olive oil or vaseline.

I have not yet seen a wound break down which was healed by the use of scarlet red or amidoazotoluol, although some of the cases have been under observation for over two years.

A grayish membrane is often seen on the granulations after the application of scarlet red ointment. I have not observed this formation following the use of amidoazotoluol.

Thiersch and Reverdin grafts are sometimes tremendously thickened following early dressings with these substances, but this thickening disappears within a few weeks.

At times it is advantageous to apply either ointment directly to the wound and then expose to the sunlight and air.

Scarlet red and amidoazotoluol gauze is prepared by saturating gauze with a 4 per cent or 8 per cent alcoholic solution of the substances and then allowing it to dry.

The substances can be used as a dusting powder by the addition of 4 per cent to 8 per cent strength, to boric powder. I have also tried the full strength powder on a few wounds without irritation. The effect of the scarlet red and amidoazotoluol used in this way is very rapid drying up of the wound and the formation of a tough scab under which the healing takes place.

A simple and satisfactory method of preparing scarlet red and amidoazotoluol ointment is to rub up the substance with a small amount of almond oil until the mass is smooth, and then mix this mass thoroughly with the base.

Both these ointments can be sterilized without interfering with their stimulating properties.

As a rule there is no toxic effect either from scarlet red or amidoazotoluol. Gurbski reports the only case in which any general toxic effect was noted, as follows:

A child, 11 years old, was severely burned by an explosion of turpentine. The lower two-thirds of the thigh and the entire leg to the ankle were involved. After the granulations had formed Gurbski applied 8 per cent amidoazotoluol ointment. Fifteen hours after the application the patient, who had previously been in very good health, began to complain of headache and dizziness. This was followed by violent vomiting and gastralgia. The pulse rose to 110 and was of low tension. The temperature rose to 102.3° F. There was cyanosis of the lips and albumin in the urine.

The dressing was removed and the patient placed on a milk diet. In a few hours all of these phenomena disappeared. Eight days later amidoazotoluol ointment was again applied and the same symptoms reappeared with the exception of the albuminuria. A third dressing, five days later, caused the same symptoms except that the vomiting was less marked.

During the rest of the treatment he applied the ointment to

only one-fourth of the wound at a time, and the toxic symptoms did not again occur. Rapid healing followed.

Gurbski thinks the poisoning was due to the amido group in the amidoazotoluol.

I have dressed very large granulating areas for some time with these substances without any deleterious effect.

In this connection an observation by Stoeber is of interest. He says that it is not uncommon to have bladder disturbances among the men who work in the manufacturing of dyes. This trouble is principally among the workmen occupied in the manufacture of amido combinations of benzol and naphthalin, or in factories where these products are used. The disease is characterized by cyanosis,, vertigo and weakness, strangury and bloody urine. In addition to the above symptoms, in long continued handling of these dyestuffs, hemorrhages and tumor formations in the bladder are observed. None of these symptoms have been noted following the clinical use of scarlet red or amidoazotoluol, except as noted above.

The consensus of opinion is that there is no danger of producing malignant growths by the clinical use of these substances. My own experience has convinced me of this, and although occasionally there is an overgrowth of epithelium, this soon assumes the level and the appearance of the normal skin.

Some authors have gone so far as to state that by the use of scarlet red and amidoazotoluol the majority of skin grafting can be eliminated. This is too broad a statement, but there is no doubt that wounds can be healed by these compounds which could not otherwise be satisfactorily closed except by grafting.

Scarlet red and amidoazotoluol will not heal every wound, but in the majority of cases, when applied with the proper technic, they will cause epithelial stimulation in the edges of the most sluggish wounds, and give a rapid healing which is stable and resistant, and which has the macroscopic and microscopic appearance of the normal skin. There is no tendency to subsequent contraction, and the skin becomes movable on the underlying tissues in a reasonable time. Any one of these characteristics would make the use of these substances well worth trying.

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ON CERTAIN LIMITATIONS IN INTERPRETING THYROID HISTOLOGY

By DAVID MARINE, M. D., and C. H. LENHART, M. D.
Cleveland, Ohio.

(From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.)

Any discussion of the limits of histological variation within which a thyroid gland—whether mammalian, avian, reptilian, amphibian or piscine—may be considered normal is largely of academic interest.

It has long been recognized and frequently emphasized by us that the thyroid tissue is extremely labile—reacting quickly to relatively slight physiological variations in the body metabolism and for this reason may show even daily histological changes within narrow limits. The knowledge of this fact, as applying to the thyroid just as truly as to the blood tissue, has made it unnecessary to write long papers to attempt to define in fixed and exact language the strictly normal thyroid or blood tissues. The thyroid tissue being exceedingly active and well endowed with the power to undergo hypertrophy and hyperplasia, one may observe in any animal group insensible gradations in epithelial hypertrophy and hyperplasia from the smallest amount of thyroid tissue compatible with normal body function (the normal) up to marked degrees of thyroid overgrowth. With such gradations in hypertrophy and hyperplasia it is clear that a histological standard of normal must be, within narrow limits, somewhat arbitrary and this fact explains why different observers have adopted somewhat different standards. It has long been evident that a standard of normal could not be ascertained purely by the histological examination of glands taken at random. In the case of mammals the best way to obtain an accurate conception of the least amount of thyroid tissue compatible with normal body function (the normal) is to give minute doses of iodin to a pregnant bitch throughout the pregnancy and after birth to continue the same with the pups up to the sixth month of extra-uterine life; then examine their thyroids histologically, estimate the iodin contents and the relation of the thyroid weight to the body weight. Even then one may not find all the thyroid follicles containing colloid of uniform staining reactions or the lining epithelium of uniform shape and size. One will find that the variations are slight, considering that the measuring rod is unusually delicate as compared with that of most body tissues.

From our six years' experience with the anatomy, the physiology and the chemistry of the thyroid tissue in all the

classes of animals and their orders from the cyclostomes to man we have adopted the low cuboidal epithelial cell as most nearly conforming with the normal type of thyroid epithelium although this type of gland cell may be depressed to a still lower degree of physiological activity following prolonged iodin administration or in senile states.

The above remarks while drawn particularly from work on the mammalian thyroid have been found to apply as well to the piscine thyroid. Zoological literature contains many excellent descriptions of the histology of the fish thyroid and in them one notes the same variations in anatomical structure that have so long been known for the mammalian thyroid. Our experience with the thyroid of Teleosts (bony fish) comprises a rather extensive acquaintance with 93 species and we have also noticed great differences in the histological appearance of the thyroid epithelium even in fish living wild in the streams, lakes and oceans. It has been ascertained by experiment that the thyroid changes do not take place so rapidly in the fish as in mammals, but the range of histological variation is just as great and the still more recent studies in comparative pathology of the thyroid gland have shown that in artificially reared carnivorous fish (the trout and salmon particularly) the thyroid is capable of relatively as great overgrowth as in any other order of vertebrates. This excessive overgrowth which has thus far been observed only in artificially reared fish has of late created much interest on account of the expressed views of several observers, that it is carcinoma. This conclusion is based on the fact that the thyroid overgrowth presents the histological appearance of invasion of the surrounding structures (bone, muscle, cartilage, etc.). In some recent publications [1] we pointed out that, owing to the absence of any capsule and the normally wide distribution of the thyroid follicles in fish, invasion did not have the same significance as it would have in circumscribed and encapsulated tissues and in tissues less well endowed with the power of hypertrophy and hyperplasia, and that in view of these facts other criteria than histological appearances must be provided before a frank diagnosis of cancer could be made.

In a paper by Gudernatsch [2] he rather infers that we claim the priority for pointing out the fact that the thyroid gland in fishes was not encapsulated. This was not our intention as excellent accounts of the fish thyroid in a great many species are to be found in literature [3] dating back as far as 1844, and for that reason we wished only to emphasize the fact that in a non-encapsulated tissue like the fish thyroid any overgrowth might give the histological appearance of cancer without actually being cancer. Experimental work with this overgrowth has amply justified that assumption.

In this connection we wish also to correct a misquotation that appeared in the above mentioned article as follows: "Thus Marine and Lenhart's statement that the normal follicles invade the bones is not appropriate, etc." We have never made such a statement nor could any one read into our descriptions of the normal fish thyroid such an interpretation without distortion. This author further states "In their paper Fig. 6 demonstrates this fact [that normal follicles do not invade bone] definitely, although it is supposed to show a true invasion." The author has evidently completely missed the point we wished to picture as the legend for this illustration clearly states that it represents the effect of iodin on the marked hyperplasias, i. e., the return or involution of the active and extreme epithelial overgrowth to its colloid or resting state. In this given fish the thyroid tissue had invaded bone, muscle, cartilage and had grown up to and elevated the pharyngeal mucosa. There was also extensive absorption of bone and erosion of cartilage which the microphotograph in question does not picture.

In another instance the author does not grasp the meaning we wish to convey when he says "if all glands, the follicles of which spread out far from the main bulk even into the gill region, are highly hyperplastic, then, according to Marine and Lenhart, the colloid material should be nearly or entirely absent in them. Yet it is present throughout the gland." There are all degrees of active epithelial hyperplasia and as the colloid content (as determined by staining and estimating the iodin content) in general varies inversely with the degree of active hyperplasia there are also all degrees of lessening of the colloid content. Now after extensive hyperplasia has taken place and the thyroid tissue has infiltrated all the surrounding structures including extensions into the gill arches, recovery may take place either spontaneously or from iodin administration, i. e., the active hyperplasia may cease from further growth and the epithelium return to a cuboidal form with the filling up of the follicles with colloid. This recovery implies the return to the colloid or resting state or the nearest normal state that such a thyroid can assume. The distribution of these now colloid follicles is, of course, just as extensive as when these same follicles were in their actively hyperplastic state, i. e., if the follicles have invaded bone, muscle, gill arches, etc., during their actively hyperplastic state they will remain in these locations throughout the life of the fish although the epithelium becomes cuboidal instead of columnar and the colloid content increases to the normal amount. In other words physiological recovery from the condition producing thyroid overgrowth (goitre) does not and cannot entail an absorption and disappearance of the follicles.

Just as there are slight departures from follicular uniformity as regards epithelium and colloid content in the normal thyroid so also in the actively hyperplastic thyroid the follicles show variations in the size of the epithelial cells and in the colloid content relatively more marked than obtains

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[1] Johns Hopkins Hosp. Bull. 1910, XXI, 95; J. Exper. Med., 1910, XII, 311; J. Exper. Med., 1911, XIII, 455.

[2] Johns Hopkins Hosp. Bull., 1911, XXII, 152.

[3] Simon, J.: Philos. Trans. Lond., 1844, Pt. 1, 295; Baber, E. C.: Philos. Trans. Lond. 1876, Pt. 2, CLXVI, 557; and *Ibid.*, 1881, Pt. 3, CLXXII, 577; Maurer: Morphol. Jahrb., 1885, XI, 129; Dohrn: Studien, XII, Mitteil. Zool. Stat. Neapel., 1887, VII, 301; Mueller, W.: Jenaische Zeitschr., 1871, VI, 428; Mackenzie: Proc. Canad. Inst., 1884, 134; Thompson, F. D.: Philos. Trans. Lond., 1910, Series B, CCI, 91.

in the normal. These variations are not possible of a definite explanation at present, although it is probable that they are in part dependent upon the blood supply, the lymphatic drainage and perhaps upon other methods of interference with the follicle's nutrition which modifies the cells' activity. Thus it is well known that in secondary hyperplasia (hyperplasia occurring in a colloid gland) the peripheral or subcapsular zone undergoes hyperplasia earlier than the central portion and Ribbert[4] has shown in the experimental regeneration of dogs' thyroids following partial removal that the peripheral zone shows hypertrophic changes earlier than the more centrally placed follicles.

These points are mentioned to show that in any phase of the histology of the thyroid one may place a too literal interpretation on slight variations in this very labile tissue which could not be detected at all in tissues less well endowed with the power of hypertrophy and hyperplasia. It is the general and predominating type of changes throughout the gland and not the accidental condition present in certain follicles that determine the state of the gland so far as functional activity is concerned.

[4] Virchow's Archiv f. path. Anat., 1889, CXVII, 151.

PNEUMOCOCCUS PERITONITIS.

WITH REPORT OF A CASE.

By HARVEY B. STONE, M. D., Baltimore.

Pneumococcus peritonitis, not as a pathological finding, but as a clinical entity, presents a fairly well defined symptom-complex, which should be better known and more generally recognized than is the case at present. Although not one of the exceedingly rare diseases, it is still sufficiently infrequent to deserve reporting. These are the reasons which lead to the presentation of this paper, reinforced by certain features of this particular case which seem of unusual interest.

The facts in the case are as follows:

Patient of Dr. Jeffries Buck, female, 5 years old, white.

Family History.—Not significant.

Past History.—Measles, whooping-cough, chicken-pox, pneumonia two years ago, complicated by acute otitis media. After recovery from pneumonia, the otitis persisted and became chronic with frequent exacerbations of earache and discharge. The last of these flare-ups was on March 26, when the child cried at night with earache, was feverish, and awoke the next morning with considerable discharge from the left ear.

Present Illness.—On the morning of March 30, following an indiscretion in diet of the previous evening, she was seized with sudden severe abdominal pain and vomiting. There was also fever and diarrhœa, the stools being of an exceedingly offensive odor. It should be noted that other members of the family also suffered from somewhat similar gastro-intestinal upsets, but without fever being noted, and with rapid return to normal.

The child did not improve. The fever and the abdominal pain, which was generally distributed, but most acute at the umbilicus, and the diarrhœa persisted, in spite of calomel given to clear up any chemical source of disturbance in the intestinal canal. On March 30, the temperature reached 104.5° F. On March 31, Dr. Buck noted some fullness and tenderness of the abdomen with persistence of the former symptoms and requested a surgical consultation.

Physical Examination.—5 p. m., April 1. Child sleeping. Temperature now 102° F., pulse 120, respiration 30. No visible discharge from either ear. Lips dry and cracked. Tongue coated. Child awakened, but remained notably apathetic and continued so during the illness.

Chest.—Heart clear. Lungs entirely negative.

Abdomen.—Slight symmetrical distention in lower half. Respiratory movements limited to chest and upper abdomen. No visible peristalsis. On palpation, general tenderness all over abdomen, most intense below level of umbilicus, but no difference between the two sides. No particular tenderness over appendix region. No masses felt. It was noted that rigidity was slight, much less than the other findings seemed to justify, and that the patient persistently referred the worst pain to the navel. Slight muscle spasm.

On percussion, no areas of dullness were noted. The liver dullness was pushed up about two fingers' breadth above the costal margin.

Rectal Examination.—Rectum ballooned. Tenderness all over vault of rectum. Pelvic organs felt normal. Vaginal discharge noted, which was later stained and showed Neisser's organisms. In this connection it should be noted that the child slept with an aunt who was known to have pelvic inflammatory disease.

As a result of the examination, there was a very definite impression obtained of some intra-abdominal trouble that might require surgical intervention. The picture was certainly not that of any of the usual lesions, however. Appendicitis, some form of obstruction, pelvic inflammation, and other conditions were considered unlikely, and it was felt that the case was obscure and unusual. As the child's temperature had come down two degrees, and the vomiting had ceased for several hours, and there seemed a general improvement, operation was not urged, but the child was placed in the Hebrew Hospital under observation. During the night, the temperature rose again to 104° F., the vomiting recommenced, tenderness and pain became greater, and the leucocyte count was found to be 18,400. An immediate exploration was decided upon in the morning.

Operation.—Through a right rectus incision the abdomen was opened, and at once thick greenish-yellow pus welled out, which resembled condensed milk quite closely in color and consistency. It was noted that the pus was odorless. A rapid search of the pelvis, the appendix, the gall-bladder, stomach and small bowel was made. No lesion accountable for the infection could be found. Everywhere the same pus, with numerous thick flakes of fibrin was found. The serous surfaces were noted as being much less injected than one would expect with so much free exudate. There was absolutely no walling off or abscess formation, every surface inspected being bathed in free pus. A diagnosis of probable pneumococcus peritonitis was made on the character of the pus and the absence of a definite visceral lesion. Cultures were made and stained slides were sent to the laboratory for examination. Gonococcal peritonitis was considered improbable as the pathological findings at operation all pointed against it. Closure of the abdominal wall, leaving space for free drainage, concluded the operation.

Bacteriological Report.—Pus from the abdomen showed a Gram-positive, encapsulated organism occurring in pairs and short chains; considered pneumococcus. A culture and smears made from the left ear immediately at the conclusion of the operation were negative. No discharge from the ear was visible at this time. A stain was also made from the vaginal discharge which, as noted above, showed Neisser's organisms—biscuit-shaped, intracellular Gram-negative diplococci.

Post-operative Course.—For a short time the patient seemed to rally, but the evening of the day of operation, her temperature rose steadily, she became delirious, and died the next day with all the symptoms of a profound intoxication, the temperature having reached 106.2° F., pulse 170. Post-operative treatment consisted in the same measures adopted for peritonitis in general—the Fowler position, the Murphy rectal saline solution, nothing by mouth, frequent subcutaneous infusions of normal salt solution. No autopsy was secured.

These are the general facts of the case. There are one or two features worthy of comment and a brief survey of the subject as a whole may not be out of place.

In the first place, here is a case of what has undoubtedly in the past been called "primary," "idiopathic" or "cryptogenic" peritonitis. Careful questioning, however, elicited a history of pneumonia two years before, with a complicating otitis media, the persistence of this otitis in the interval, and finally an acute flare-up of considerable intensity a couple of days before the onset of a peritonitis caused by pneumococci. Such a series of incidents is, of course, strongly suggestive. It is to be regretted that efforts to secure bacterial evidence from the ear were unsuccessful.

A second interesting point is the laboratory report of pneumococci from the peritoneum and gonococci from the vaginal discharge. An almost identical case was found reported by Dudgeon and Sargent,[1] who comment on this coincidence with a warning that the finding of specific organisms in the vaginal secretion of such a child does not necessarily mean the existence of a gonorrheal peritonitis. A third fact of note is that this case presents a very typical example of one form of pneumococcic peritonitis, and were such cases not so uncommon the diagnosis would not be extremely difficult before operation. In order to substantiate this statement a summary review of the subject is necessary. No attempt will be made at an exhaustive report of the literature, which is now quite extensive, although the disease is comparatively rare.

The disease was first described by Bozzolo[2] in 1885, as an autopsy finding, and first operated on by Sevestre[3] and Nélaton[4] in 1890. Since then numerous isolated cases have been reported, a number of extensive reviews of the subject have been published, and several theses and monographs written. In 1903 von Bruun[5] collected 57 cases occurring in children and 15 in adults. Jensen[6] published an exhaustive article in the same year. Annand and Bowen[7] in 1906 collected all the cases in children published up to that time, finding 91 under 15 years of age. In the same year von Robbers[8] reviewed the history and literature of the condition. Since 1906, in an extensive but not exhaustive review of the literature, 30 cases have been definitely recognized as pneumococcus peritonitis, while a number of papers have probably dealt with this condition, though unrecognized, under titles such as "Peritonitis without ascertainable cause,"[9] "General purulent peritonitis without obvious cause,"[10] etc.

Pneumococcus peritonitis occurs with marked preponderance in children, and especially in the female sex, between 2 and 14 years of age. Various authorities differ as to the explanation of this incidence of the disease, but all agree as to the facts.

Etiologically, the disease, of course, represents a specific infection of the peritoneum, but much discussion has risen as to the portal of entry. Two groups of cases are usually recognized: the primary or idiopathic, and the secondary, in which the peritonitis is obviously consequent to some pre-existing pneumococcic lesion elsewhere. Of such lesions, pleuro-pneumonic involvements are naturally by far the most common, and next to these, in frequency, is otitis media. The recognition of a "primary" form as a distinct group does not seem logical. It simply means that the portal of entry, instead of being obvious as in a precedent pneumonia, is obscure. The modes of transmission accepted as proved by various writers embrace operative infection, transmission by blood and lymph streams, and direct penetration, with or without perceptible lesion, of the diaphragm and the walls of the gastro-intentinal canal.

Clinically the cases fall into two fairly distinct groups—the encapsulated and the diffuse forms, each of which presents a characteristic picture. The encapsulated form begins with a sudden onset, in a number of cases following an indiscretion in diet, with acute abdominal pain, vomiting and fever. In an overwhelming majority of cases, but not in all, there is diarrhœa generally characterized by the very fetid odor of the stools. The local abdominal signs at this stage and in this form are not very pronounced. The vomiting stops in from 12 hours to a few days. The fever, never very high, persists from 8 to 10 days. The diarrhœa is the last of these early symptoms to cease. After ten days or two weeks, local abdominal disturbances become more pronounced. The pain, which may have stopped, begins again, and instead of being general, becomes localized, nearly always in the hypogastric region. Fullness, gradually but steadily progressing, is noticed. Over this distended area dullness on percussion, fluctuation, and occasionally œdema of the abdominal wall develop. These symptoms, again accompanied by fever, become more pronounced, and unless interrupted by death or operation, a spontaneous rupture nearly always through the umbilicus affords escape for the pus. Three stages may thus be recognized—peritoneal invasion, accumulation of exudate, and spontaneous rupture. The prognosis in this form, which undoubtedly represents a relatively benign infection, is good. Annand and Bowen report 86 per cent recoveries in 45 cases of this type.

In the diffuse form of the disease, the symptoms of onset are the same—sudden abdominal pain, vomiting, diarrhœa, fever—but they are all much more intense than in the local-

izing type of infection. The fever, which is perhaps the most objective sign, is always quite high, often ranging well above 104° F. In these cases the virulence of the infection is much greater than the natural defence of the individual. Death may occur in 24 hours. Where the course of the disease is less abrupt, there is often a brief apparent improvement at the end of about 48 hours. In a short time, however, the symptoms grow more marked, abdominal distention, tenderness, perhaps movable dullness become apparent. In short, the picture of peritonitis develops, with interesting qualifications, rigidity as a rule being far less marked than the other symptoms would seem to justify, and there is diarrhœa instead of constipation. There is a high leucocyte count, very elevated temperature and profound toxæmia. The prognosis is exceedingly grave. No such case has survived unless operated on. Annand and Bowen, in 46 cases, 18 of which were operated on, record only 6 recoveries, 14 per cent.

The pathological findings, aside from the determination of the specific organisms, consist in the character of the exudate. This is, in most instances, thick, creamy, greenish-yellow, and odorless. In a few cases, however, the pus has been described as profuse, thin and of a turbid, dirty brown color. In either form the presence of numerous flakes and deposits of fibrin is characteristic. Several writers have noted that the degree of injection of the peritoneal surfaces seemed slight in proportion to the amount of exudate present.

The treatment of any form would seem to be immediate laparotomy and drainage, for the obvious and time-honored purpose of evacuating pus. There are, however, a few dissenting voices from this opinion. Thus Nobécourt[11] thinks it unwise to operate too early, as in all cases surviving the first few days the infection will localize and then there is less danger, in his opinion, of its being spread by the operator. Manifestly this is simply leaving unaided nature to fight its own battle, and if it wins, doing nothing more than forestalling the spontaneous discharge of the pus. The cases which succumb are not given the best possible chance, by which some of them, at least, would be saved. Naturally the prognosis is better in cases first seen in the stage of localized abscess, but nothing is gained and much may be lost by allowing early cases to wait in hopes that walling off will occur.

To summarize: Pneumococcus peritonitis occurs more often in children than in adults, and more often in female than male children. There are two forms: the encapsulated, which exhibits a first period of invasion, a second period of localized abscess formation, and a third of spontaneous rupture of the abscess; and the diffuse form of general peritonitis rapidly fatal unless operated upon. The symptoms of onset in both forms, varying only in intensity, are abdominal pain, vomiting, fever, and diarrhœa. Rigidity is not characteristic. The treatment is surgical intervention as soon as possible. The prognosis of the diffuse form is very bad; of the localized form, fairly good. The pus is characteristic, and often sufficient for diagnosis from its macroscopic appearance alone.

In conclusion, I wish to express my indebtedness to Dr. Ney, of the Hebrew Hospital, for his kind assistance in placing the hospital records of the case at my disposal.

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AN ANOMALOUS DUCT BELONGING TO THE URINARY TRACT.*

By Paul G. Woolley, M. D.,
Professor of Pathology, University of Cincinnati,
and
Herbert A. Brown, M. D., Cincinnati.
(*From the Laboratories of the Cincinnati Hospital.*)

The specimen we wish to describe is of unusual interest because of its extreme rarity, for, in spite of a somewhat painstaking search of the literature we have found no account of any similar condition. It was found during the post-mortem on a patient in the Cincinnati Hospital (No. 153426) who had been admitted for cutaneous blastomycosis, and who died of the generalized form of that disease.

Because none of the symptoms of the patient could be referred in any way to the condition of the genito-urinary tract we shall omit the history and the report of the autopsy, and confine ourselves to an account of the condition only as it referred to the specimens. We believe that the case has been discussed from the dermatological standpoint by Dr. Ravogli.

The left kidney weighed 200 gms. The capsule stripped with slight difficulty and left a moderately roughened, almost nodular surface. The cut section was rather pale, and the line of demarkation between cortex and medulla was indistinct. The cortex was of about normal thickness. The blood vessels were sclerotic. The right kidney showed the same general appearance. The left adrenal showed a somewhat evident hyperplasia of the medulla. The right adrenal was apparently absent.

* Read before the Cincinnati Society of Medical Research, May 4, 1911.

Extending from the antero-mesial aspect of the upper pole of the right kidney, that is, from the normal site of the right adrenal, appeared a distended, tortuous, saculated tube, which ran parallel with the right ureter which it finally passed to enter the posterior surface of the prostate (Fig. 1). The average diamater of this sac was about 2 cm. In its wider parts it was distended to about 4-5 cm. At its lower end it was rapidly constricted, almost to occlusion. Through the lower end a fine probe could be passed into the posterior urethra at the site of the sinus pocularis. In the immediate vicinity of the prostatic part was a blastomycotic abscess which involved, to a minimal extent, the wall of the duct. The upper part of this distended duct ended in a mass of tissue of about 2 x 1 x 1 cm. in size, which was taken to be the remains of an atrophic adrenal and which later proved to contain only one small area which in anyway resembled adrenal tissue. This mass also contained abscesses. There was no connection whatever between the tube and the kidney, ureter or bladder. The pelvis of the kidney was not dilated. Both testicles were present and had undergone descensus.

In the expectation that sections of the specimen would be of some asistance, bits of tissue were taken from the nodule of tissue at the renal extremity, from the sac at its origin near this renal nodule and from the prostatic portion of the tube. The blocks of tissue taken from the uppermost part included the nodule itself and the kidney so that comparison could be made in the same section.

The sections made from these blocks can, for the purposes of description, be divided into three parts; one, representing the mass of the nodule; a second representing the kidney; and a third, the boundary zone between nodule and kidney.

The tissue of the first part was for the most part well-formed fibrous tissue enclosing large and small cystic spaces, large and small blood vessels, nerves, collections of epithelial cells (columnar, as a rule, occasionally cubical), which seem to represent cross sections of ducts (Fig. 6), and blastomycotic abscesses. The larger cystic spaces were lined with a single row of cuboidal epithelium and filled with a granular albuminous material in which masses of desquamated epithelium, polymorphonuclear leucocytes, giant cells, and blastomyces, were imbedded. The smaller cystic spaces were of two particular forms. One form was lined with one or more rows of cylindrical or high columnar epithelium and filled with desquamated cells, cellular detritus, leucocytes, and extra- and intra-cellular blastomyces; the other was lined with one or more layers—usually a single layer—of cuboidal epithelium and contained a material that resembled thyroid colloid (Fig. 4). Occasionally this colloid showed concentric lines and in some cases it was so changed that it stained with basic dyes and appeared quite similar in appearance to the corpora amylacea of the prostate (Fig. 5). As a rule, however, they were rather more irregular than the ordinary prostatic corpora amylacea, and had a striking resemblance to other similar bodies that are occasionally present in the ovary and other organs. The blood vessels had, as a rule, thickened walls and in the majority of instances showed endothelial prolifieration, even, in some cases, to the point of obliteration. The nerves showed no abnormalities, either in cross or longitudinal sections. No ganglion cells were observed.

The tissue of the second part represented merely a narrow zone of kidney tissue in which there were general changes that taken collectively indicated a chronic diffuse nephritis of moderate severity.

The boundary zone between the two parts already described was composed of fibrous tissue that firmly united the kidney and the nodule. This zone was of some little width, but the line of demarcation was narrow, and was represented by a narrow line of renal capsule. In but a few sections, close to the kidney, and yet separated distinctly from it were small localized masses of tissue, glandular in structure, and quite similar to the tissue that is seen in adrenal and renal adenomas, and in which was no sign of ganglion or chromaffin cells (Figs. 3 and 4).

The general impression given by these sections was that one was dealing with a possible combination of renal, adrenal, and ovarian tissue indifferently arranged. Drs. Knower and Wieman have suggested the occasional resemblance to a Wolffian body.

The sections from the sac itself at the upper and lower ends show that the walls of the sac were composed of fibrous tissue with a minimal number of smooth muscle fibers and were lined with low columnar or cuboidal epithelium (Fig. 7).

There are, under more or less normal circumstances, possibilities of but three openings into the prostatic urethra—two, the openings of the ejaculatory ducts, which were present in this case, and one, the opening of the united Müllerian ducts.

There is also the theoretic possibility that as a result of embryonic developmental variations as suggested by Pohlman the ureter might open into the prostatic urethra. Pohlman says that in changing its position on the Wolffian duct from dorsal to lateral, at which time the ureter comes to open distinct from the Wolffian duct and would naturally open in common with it or into parts developed from its lower end, or "the ureter might open laterally to the Wolffian duct and on a level with it. The opening in this case would be found in the prostatic urethra."

If this be a true explanation, then the mass of tissue above the kidney is the remnant of an atrophic or hypoplastic kidney, or it is the remains of the Wolffian body. In the former case we should be dealing with a unilateral multiplicity of kidneys, each with its ureter, one of which opens into the prostate; in the latter we should have to consider that the duct was the result of persistence of the united Wolffian duct and ureter.

There is the other possibility that in this case we are merely dealing with an abnormal course of a complete ureter without any participation of a Wolffian duct, as occasionally happens in cases with accessory ureters. It is to be noted that in such cases the one of the ureters, usually the one which

FIG. 1.

FIG. 2.

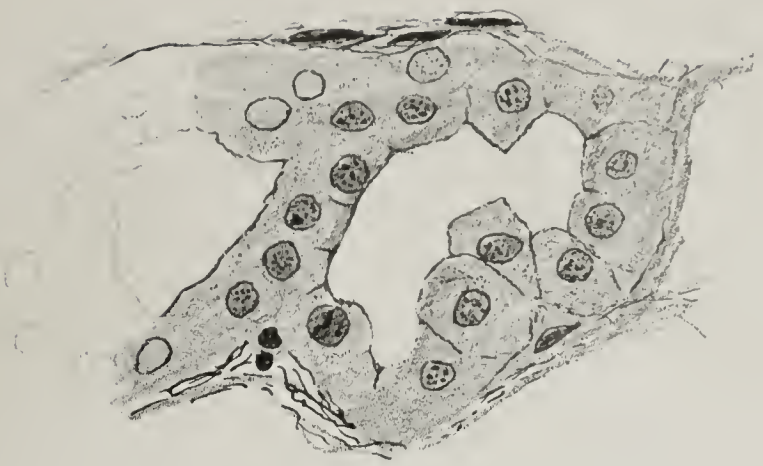


FIG. 3.

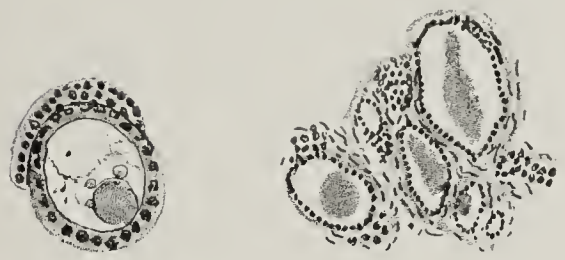


FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

has the superior origin, lies deeper and may open into the colliculus seminalis, the vas deferens or the seminal vesicle. In any case we cannot account for absence of the adrenal except on the basis of aplasia, or perhaps—if the nodule mentioned above be adrenal—hyperplasia. Either of these results, it might be suggested, may be the result of the development of accessory renal tissue at the expense of adrenal. The embryonic relationships of the urogenital organs are so close that the possibilities of variations are very numerous. Marchand emphasized this from the side of the genito-adrenal organs when he suggested that variations in the sizes of adrenals and ovaries cannot be considered as purely fortuitous.

It is our misfortune that the anatomic evidence at our disposal is not sufficient to permit us to come to any decision as to whether we are dealing with the result of one or the other of the possibilities mentioned.

LITERATURE.

Pohlman: *Amer. Med.*, 1904, 987.
Marchand: *Intern. beiträge z. wissensch. Med.* Virchows Festschrift. Bd. 1.
Aschoff: *Pathologische Anatomie.* Jena, 1909, Bd. 11, S. 506.
Kaufmann: Specielle Pathologische Anatomie. Berlin, 1907, S. 773.

ILLUSTRATIONS.

1. A photograph of the gross specimen.
2. The adrenal (?) rest.
3. Same as 2, enlarged.
4. Cystic spaces showing colloid.
5. Cystic space showing corpus amylaceum.
6. Ducts in the nodule above the kidney.
7. Wall of the large duct.

All of the illustrations except 1 and 3 were drawn with a camera lucida at table height using a Leitz ocular IV and obj. 3. Figure 3 was drawn with a Leitz ocular IV and a Spencer 4 mm. A. 0.80 objective.

ACUTE CHOLECYSTITIS WITH LARGE AMOUNTS OF CALCIUM SOAP IN THE GALL-BLADDER.

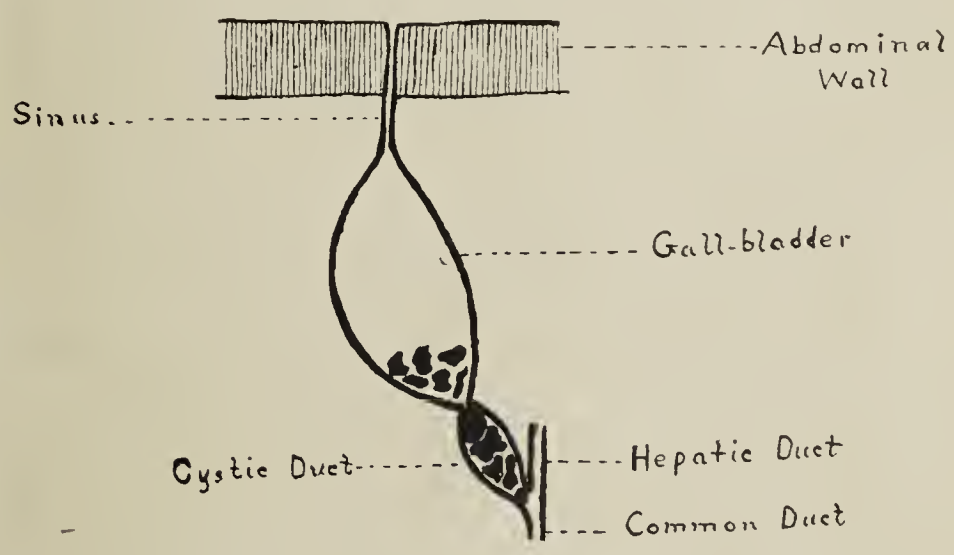
By JOHN W. CHURCHMAN, M. D.,
Late Resident Surgeon, The Johns Hopkins Hospital.

In view of the great frequency with which the gall-bladder is drained under conditions identical with those present in the patient whose case is here reported, the absence of any similar case in the clinical literature emphasizes the uniqueness of the observation here made. Moreover—though soaps are found in small amounts in the bile—I have been able to find no reference, in the chemical literature of the subject, to a gall-bladder contents composed almost entirely of soap.

There was nothing unusual about the clinical features of the case. The patient presented the typical picture of an acute cholecystitis. She had never had typhoid fever. The illness began two days before admission with chills, fever, and a general aching. Delirium appeared that night; and the next day there was abdominal pain—at first general, later localized in the right side and radiating to the right shoulder. Nausea and vomiting were present, but there was no jaundice. The physical signs were those of acute cholecystitis. The gall-bladder was not palpable. The liver was slightly enlarged.

At the operation straw-colored fluid was found in the peritoneal cavity, cultures from which remained sterile. The appendix was normal, but the gall-bladder was distended and much inflamed. After isolating it with gauze, it was aspirated; but instead of the pus which was expected a fluid, unlike anything previously seen in the gall-bladder, appeared in the barrel of the syringe. The color of this material but more particularly its strange odor (suggesting a mixture of cod liver oil and turpentine) recalled the contents of a mesenteric cyst operated on a few days previously; and it was for a moment uncertain whether what had been supposed to be gall-bladder might not prove to be a cystic growth of the liver. On opening it, however, a large number of bile-stained stones were found and removed. There was neither bile nor pus in the gall-bladder. The cystic duct was completely blocked by stones. The contents of the distended gall-bladder consisted entirely of a material like that which had been aspirated. The gall-bladder was drained in the usual manner. Convalescence was without event. Three small stones were found in the tube at the first dressing. The discharge from the biliary fistula was at first brownish, later purulent, then thin and mucoid; but it never contained bile.

The wound healed to a pin-point opening, through which



the limpid mucoid material, characteristic of hydrops, continued to drain. The sinus persisted, causing the patient almost no inconvenience, but discharging at intervals. After a year had elapsed, she returned to have it closed. At this operation, the gall-bladder contained much clear mucoid fluid (from which no organism could be grown) and a few facetted, pigmented stones. The distended cystic duct contained many gall-stones and communicated with the gall-bladder by an opening so small that the stones could only with great difficulty be delivered into it. (See diagram.)

The common and hepatic ducts contained no stones. The usual drainage was carried out. Bile appeared in the sinus on the seventh day and soon became profuse. The wound closed promptly and has remained healed.

The strange material removed from the gall-bladder at the first operation was grayish-white in color, glistening, opaque in mass, but slightly translucent in thin layers. It was fluid enough to run into a large aspirator, but its consistency was somewhat that of tooth paste and it could be picked up in mass. It had no property of adhesion whatever, and when handled, failed to come into intimate contact with the skin of the finger, from which it was separated, apparently by a thin layer of oil. None of it stuck to the finger, though its peculiar oily odor remained on the skin. It was ductile and could be pulled out in strands, like pulled candy; but it was somewhat elastic.

An agar slant was inoculated with some of the material and *B. typhosus* grew out in pure culture. The patient's Widal reaction was taken and found positive. It is interesting that cultures made from the gall-bladder at the second operation, one year later, were negative.

A chemical analysis of this material (kindly made by Dr. Slagle) showed it to consist largely of soaps of the calcium salts. Some free fatty acids were also present, but no bile pigments.

There is nothing in the secretion of the gall-bladder proper from which the soaps here present could have originated. This secretion has been carefully analyzed in two cases presenting biliary fistulæ and occluded cystic ducts, and the following composition found.[1]

[1] Birch and Spong: Journal of Physiology, Cambridge, 1887, VIII, 378.

Water and gases		979.7
Solids		20.3
Organic	Mucin Albumin (a trace)	12.09
Inorganic	Chloriue. Carbon dioxide. Sodium (combiued with chlorine). Sodium (combined with CO_2). Potassium salts and phosphates.	

These findings agree with other examinations of the gall-bladder secretion.

Hammarsten's analyses of the bile in the liver and in the gall-bladder showed the fats, soaps and fatty acids to be more abundant in the latter situation. His figures are as follows:

COMPOSITION PER 1000 PARTS OF BILE.

The averages of Hammarsten's figures are here given approximately.

	Liver Bile.	Gall-bladder Bile.
Water	About 970	About 835
Solids	" 30	" .165
Muciu and Pigments	" 5	" 42
Taurocholate	" 3	" 23
Bile acids and Alkalis	9+ to 18+	87 to 96
Glycocholate	6+ to 16+	67 to 69
Fatty Acids and Soaps	1+	About 11
Cholesterin	.6 to 1.6	" 9
Lecithin / Fat	.2 to 1.5	4 to 7
Soluble Salts	6 to 8	About 3
Insoluble Salts	.2 to .5	" 2

The analyses of other investigators, though the figures have shown some differences from those of Hammarsten, agree as to the substances found and, in an approximate way, as to their relative proportions. All observers have found a small amount of fatty bodies (fatty acids, soaps, fats and lecithin), but none have found them in any such preponderance as was the case in this patient.

NOTES ON NEW BOOKS.

Progressive Medicine, Vol. I, March, 1911. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. (*Philadelphia and New York: Lea & Febiger, 1911.*)

The most important European and American articles on recent advances and theories in the treatment of the "Surgery of the Head, Neck and Thorax," "Infectious Diseases, including Acute Rheumatism, Croupous Pneumonia, and Influenza," "Diseases of Children," "Rhinology and Laryngology," and "Otology," are reviewed in this volume with the usual care and skill shown by the contributors. This work is of value to any practitioner who wishes to keep himself well informed on the progress of medicine in all its branches—a progress which is steady though sometimes necessarily slow.

A Text-book of General Bacteriology. By Edwin O. Jordan, Ph. D. Fully illustrated. Second Edition. Thoroughly Revised. Price, $3.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

As errors have been corrected and omissions repaired, which appeared in the first edition of this work, and several new sections added, its real value, to which attention was drawn in our issue of July, 1909, has been increased, and it is fortunate that students have such a useful and reliable book to guide them in their studies.

Accidental Injuries to Workmen, with Reference to Workmen's Compensation Act, 1906. By H. Norman Barnett, F. R. C. S., etc. With Article on Injuries to the Organs of Special Sense, by Cecil E. Shaw, M. D., etc. And Legal Introduction, by Thomas J. Campbell. Price, $2.50. (*New York: Rebman Company, 1911.*)

This work is more adapted to the use of the English profession than to our own, but since injuries to workmen are as frequent here as elsewhere, and since the question of the proper responsibility in such cases is steadily becoming more acute in this country, and more and more accident cases are being taken into court, it is most satisfactory that American doctors should have such an excellent book to study when they have to deal with "accidental injuries, mechanical and chemical, to the various organs and tissues of the body, including those of special sense." The treatment of such injuries properly finds no place in this work, but diagnosis is fully discussed, and also the remote effects of injuries. This is in fact a text-book to guide physicians how to study an injury which may result in a suit for damages. There

is already a large body of surgcons in this country who will find this book most serviceablc, and we are glad to be able to call their attention to it, for the author has handled his material skilfully and written interestingly. The publishers are also to be commended for the quality of the paper which makes the book light and easily held in one hand—so many publications are clumsy and fatiguing to hold.

Surgery of the Brain and Spinal Cord. Based on Personal Experiences. By PROF. FEDOR KRAUSE, M. D. Translated by PROF. HERMAN A. HAUBOLD, M. D. Vol. I. (*New York: Rebman Company, 1909.*)

In his introduction to this work Prof. Krause states that he does not attempt to offer a text book on neurology but "to present numerous ilustrations from nature which are destined to constitute an accurate picture of the status of the surgery of the brain and spinal cord as it stands at this writing." The work therefore does not take up the pathology, pathological physiology, symptomotology, and diagnosis of surgical neurological conditions, but deals with some of the surgical problems relative to these conditions and the surgical procedure used in attacking them which in the author's hands have proven most satisfactory. It is evident from his introduction that Prof. Krause still holds the view that the internist and neurologist should make the diagnoses of surgical neurological conditions for the operating surgeon; a view with which we are not at all in accord.

A book dealing with such a special branch of surgery will have a varying degree of usefulness. To the general surgeon who has had little or no special training in neurological surgery it will be of great aid, for the author has had a large experience in this branch of work and the technic he describes in dealing with various intracranial lesions is superior to that employed by the average general surgeon. To those who intend to devote themselves to neurological surgery the book will be a valuable addition, for the author has appreciated and correctly grasped many of the problems which tend to make neurological surgery a special field of work. To the relatively few who have had considerable experience in the surgery of the brain, this volume will be an interesting exposition of a single operator's technic and experiences in neurological surgery, but will offer little that is especially new.

The first 50 pages of the book are devoted to trephining, the control of hemorrhage from scalp and bone and the method of forming osteoplastic flaps in the approach to lesions in different regions of the brain. It would seem that the method of Von Hardenhain or the plates of Kredel which he employs for the control of hemorrhage from the scalp are unnecessary and time-consuming procedures. A well fitted tourniquet practically always serves the purpose. He describes various methods for controlling hemorrhage from the bone, but admits total inexperience with the most useful of methods, i. e., the use of Horsley's wax. In the formation of osteoplastic flaps he rightly, we think, advocates the use of hand-driven instruments rather than electrically-driven engines. His flaps could be improved upon; a bevelled upper edge made with a Gigli saw prevents the flap from pressing down upon the dura; and if the base of the flap is made narrow and directed downward toward the temporal region it can be fractured and the risk of injury to dura by cutting across it avoided. In agreement with many operators Krause prefers a two stage operation, the first stage ending with the formation of the bone flap. He speaks of the frequency of collapse at the end of the first stage; an occurrence which we have very rarely seen. Collapse at this time must mean undue hemorrhage although Krause states that it often occurs without much loss of blood. While two stage operations are undoubtedly necessary in some instances, we have been accustomed to see the entire operation completed at one sitting; and certainly a one stage procedure is to be preferred if it can be accomplished with no additional risk to the patient.

In exposure of the cerebellum his technic is far from satisfactory. He employs a sitting position which is not only difficult to maintain but is bad for the patient, trying to the anaesthetist and inconsistent with perfect asepsis. Certainly the position used by Cushing is greatly to be preferred. Krause makes use of a unilateral osteoplastic flap which in states of increased pressure must be a difficult and bloody procedure. The exposure of only one cerebellar hemisphere does not allow sufficient dislocation for a complete and satisfactory exploration; indeed, it is only by a wide exposure of both hemispheres tnat a complete explora tion of the cerebellum and lateral recesses is possible. Experience teaches that a lesion, such as a cyst, occupying one hemisphere may by pressure cause symptoms entirely referable to the opposite intact lobe; and therefore it is possible that a lesion might escape detection with a unilateral exposure.

His treatment of various lesions of the brain exposed at operation he describes for the most part by citing examples from his series of cases. In the main his treatment is good. He recognizes the necessity of preventing injury to vessels which may cause post-operative cerebral softening, of careful control of hemorrhage and of preventing injury to the pia-arachnoid. It would appear that he drains too frequently. He packs cyst cavities with gauze to obliterate them; we believe that every effort should be made to remove the cyst wall even though thin. He has observed the rapid obliteration of cavities left after removal of tumors or other lesions, but often drains these cavities, which, with careful control of hemorrhage, is unnecessary.

For unlocalizable lesions causing pressure symptoms he does a decompressive operation which is a modification of his osteoplastic flap operation. The objections to it are that the defect is made in a region protected only by scalp; and that it is as extensive, if not more extensive than an osteoplastic flap resection. Compared with this method the simple procedure conducted under the temporal muscle as described by Cushing would seem vastly superior; and we feel that Krause does not at all appreciate the advantages of this method. He does not make use of the method employed by Horsley.

The closure of his wounds is not done with sufficient care, and it would appear that this fact is largely responsible for the number of cases of post-operative fungus or brain prolapse which appear in the volume. Undoubtedly the complication should be less frequent. He does not apparently suture the dural flap made at operation but simply lays it back over the cortex. This seems particularly bad especially if there is increased pressure; for the cortex immediately bulges through the dural defect and adhesions, if not a fungus, result. To conduct a second operation at some future date through a wound closed in this manner would indeed be difficult. The dura must be closed with the greatest care and if any opening is left in it, this should be under some protected region, as under the temporal muscle. Sometimes even the scalp is not sutured but simply held in place with dressings. As previously stated he drains his wounds too frequently; he packs cystic cavities and those left after the extirpation of tumors—procedures which in the presence of increased pressure tend to favor fungus formation.

In all his operations chloroform is used. The operator does not wear gloves. He believes that rapidity of technic, control of hemorrhage and asepsis are the essential factors for success.

As customary in works on brain surgery he devotes many pages (20) to cranio-cerebral topography. He appreciates the difficulty of recognizing the pre- and post-central gyri even when the cortex is exposed; yet he always marks the fisures of Sylvius and Rolando on the scalp the day before operation.

He considers brain puncture and believes it a definite aid in the diagnosis of intracranial lesions. He warns however against the dangers of this procedure. He himself has had several cases of bleeding and in some others an aggravation of symptoms already

present. He mentions the possibility of causing hemorrhage into the ventricle and of encountering a vascular tumor such as an angioma. It would seem pretty definite that this procedure should be used only when the needle can be introduced under direct inspection.

He describes ventricular puncture, giving the various points of election for introducing the needle, but does not take up the indications or contraindications for this procedure. He gives the various methods for accomplishing permanent drainage of the ventricles. As a preliminary to exploration of the cerebellum in cases with extreme tension he does a ventricular puncture which is a very useful procedure.

The translation has been rightly estimated by the translator in his preface. His attempts to follow the German too closely have in many places been made at the expense of good English. The volume is elaborately illustrated with 24 colored plates, some of which are very good, others less well done and showing little detail. The other illustrations are as a whole poor. The print is large and legible with perhaps too frequent use of bold-faced type. The size of the volume is unnecessarily large. In scientific works, with few exceptions, it seems to us a mistake to publish a volume with such broad margins.

The Treatment of Syphilis with Salvarsan. By Sanitätsrat Dr. Wilhelm Wechselmann, of Berlin, with an Introduction by Professor Dr. Paul Ehrlich, of Frankfort-on-Main. Only Authorized Translation by Abr. L. Wolbarst, M. D., of New York Price $5. (*New York and London: Rebman Company. 1911.*)

Wechselmann's experience with the use of salvarsan has been larger than that of any other physician, since he was one of the first chosen by Ehrlich to try the new remedy. In this work Wechselmann gives us the result of his studies of 1400 cases treated, and what he has to say is of importance to all physicians who are using this drug. The profesion at large is now pretty well acquainted with the value, danger, and other characteristics of the medicine, but here we have an as authoritative book on the entire subject as can be had up to the present time. With the lapse of a few years after the discovery of the drug new views may be held in regard to it, but at present this book can but serve as a most valuable guide to all students, for the author has considered all the essential points in regard to the administration of salvarsan. It is well translated and the few illustrations excellent.

Cholera and Its Treatment. By Leonard Rogers, M. D., F. R. C. P., F. R. C. S., I. M. S., etc. Price, 4s. (*London: Henry Frowde and Hodder & Stoughton, 1911.*) *Oxford Medical Publications.*

Dr. Rogers has had a large experience with cases of cholera in the Medical College Hospital at Calcutta, and he has written a valuable and interesting work on this disease. The six chapters cover the following ground: 1, History of Cholera Epidemics and Their Lesions; II, Epidemiology; III, Etiology and Prophylaxis; IV, Clinical Description; V, Morbid Anatomy and Pathology; VI, Treatment. As in this country few physicians ever have the opportunity to see a case of cholera, this book is not likely to have many readers; but the student of tropical diseases will find it a useful book to have in his library, and will give especial attention to the chapter on Treatment, in which the author sets forth the results of the simple means used by him and by which he has been able to distinctly lower the percentage of mortality in his wards. He advocates the use of infusions of salt solution to lower the concentration of the blood resulting from the frequent evacuations; and also the administration of permanganate of calcium to destroy the toxins produced in the body by the cholera germs. With a combination of these two methods his results have been most favorable, and they deserve to be further tried. The author is modest in his claims as to the value of this treatment, which has at least one great merit, that it seems to do no harm, even if its importance prove less marked with further trial.

Manual of Human Embryology. Edited by Franz Keibel and Franklin P. Mall. In two volumes. Volume 1 with 423 Illustrations. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

In the introduction to this volume the editors announce their intention of adhering strictly to human embryology, and of not concealing the gaps which exist in the subject as is sometimes done. They assume rather the very praiseworthy attitude of especially pointing out these deficiencies, as in this way the gaps will be sooner filled.

Comparative embryology is largely excluded and is only introduced in the discussion of the early stages of development.

It is interesting to learn that this treatise on embryology which was projected by His and Keibel has been completed by Keibel and Mall, one of His's most noted pupils.

This is the first manual of human Embryology to be written conjointly by a number of authors, a method which has lately been frequently adopted in other books. Such books are subject to two dangers: first, a lack of unity, and secondly, repetition. These dangers have been avoided here however by very thorough editing and supervision, proved also by the fact that a careful reading of the book has shown a remarkable absence of typographical or other errors. The advantage of a multiple authorship is a greater thoroughness and accuracy of discussion, each author being especially qualified for his task by his own researches.

The reason given for an exclusive human Embryology is the importance of the subject to the physician.

Keibel in his introduction considers the historical development of Embryology, and one is pleased to note that great credit is given to that remarkable genius von Baer and also to His who laid a secure foundation for human Embryology and made possible the great advances of the last 30 years. Keibel calls attention to the spirit of co-operation which is permeating the scientific world, and acknowledges his indebtedness to many investigators. This spirit is part of a broader movement affecting educational institutions which no longer are rivals but rather coadjutors. This volume was published simultaneously in German and English, the English translation being made by McMurrich and the German by Keibel.

Keibel contributes articles on the germ cells, fertilization, segmentation, young ova and embryos up to the formation of the first primitive segment, germ layers and gastrulation and differentiation of external form.

Grosser writes on the egg membranes, placenta and menstruation.

Mall's contribution includes the determination of the age of human embryos and fetuses, the pathology of human ova and the development of the coelom and diaphragm; Pinkus discusses the development of the integument, Bardeen the development of the skeleton and connective tissues, and W. H. Lewis the development of the muscular system.

Keibel's discusion is an excellent one. He accepts Waldeyer's view that at birth or shortly after all oögonia have become oöcytes of the first order and so have before them only further growth and maturation. It is questionable whether the introduction of the term "polocyte" for "polar globule" is desirable. A fuller discussion of sex determination should be given. Keibel's statement that most observers now incline to the belief that sex is always determined in the ovum before fertilization is, in the opinion of the writer, not justified. There is considerable evi-

dence that the spermatozoon has some influence. No mention is made of the work of Morgan and Wilson on accessory chromosomes. Attention is called to the desirability of examining the oviducts in the hope of finding early embryos. Keibel critically reviews the early embryos which have been described and thinks Reichert's ovum has been detrimental to the progress of Embryology because of the wrong impressions created.

In the discussion of the formation of the germ layers he does the reader a service by stating precisely what he means by gastrulation. He defines it broadly as follows: "Gastrulation is the process by which the cells of the metazoan ovum are separated into an upper and lower layer." Attention is called to the gap which exists between Pfannensteil's embryos III and VI of the *Normentafel* of Keibel and Elze. Embryos 3, 4, and 6 of His he considers abnormal.

Grosser gives an excellent account of the method of placentation and explains his classification of placentæ, which is based on the extent of erosion of the decidua. According to his nomenclature the human placenta is a *placenta hæmochorialis discoidalis olliformis*. This is the highest type and is not yet reached by the anthropoid apes. His statement that the endometrium undergoes extensive degeneration in menstruation is, to say the least, misleading. He calls attention to the important fact that the presence of furrows in the endometrium may be indicative of pregnancy and that pathologists, bearing this in mind, may help embryologists to obtain early ova.

In speaking of the increase in size of the uterus in pregnancy, incorrect use is made of the terms Hypertrophy and Hyperplasia.

On page 99 lymph nodes are spoken of as existing in the endometrium; we think this should be "nodule," as lymph node should be used as the equivalent of lymph gland.

Determination of the age of human embryos and fetuses is discussed by Mall with his usual clearness and keen analysis. One is somewhat surprised at the statement, quoting Ravano, that ovulation occurs frequently during pregnancy. He emphasizes the necessity of a standardization of the *corpora lutea* as an aid to the determination of the age of ova, and makes the important suggestion that surgeons might materially assist in this matter by a routine examination of normal ovaries in abdominal sections.

He concludes that the balance of evidence is against the Reichert-His theory and in favor of fertilization occurring near the time of the last menstrual period. The crown-breech and crown-heel measurements are considered the best, corresponding as they do with the sitting and standing height of anthropologists.

In the discussion of the pathology of the human ovum, Mall incorporates largely his studies already published. He has found that 50 per cent of the ova of the first two months received by him are pathological, and considers the causes secondary and environmental rather than germinal. Changes in the chorion are found in a very large percentage of pathological ova, and inflammation of the decidua is regarded as a frequent cause. A classification of pathological ova is explained. He believes with Giacomini that as abortions are frequently due to pathological changes in the ova, threatened abortions should rather be encouraged than prevented, for if retained the embryos may become monsters.

He considers that the evidence from various sources including that of Experimental Teratology indicates that the causes of monstrosities are rather environmental than germinal and calls attention to the importance of treatment of the diseased endometrium in those cases where monsters have been born, to prevent a repetition. His statistics show that seven per cent of all pregnancies result in pathological ova. This discusion is a valuable contribution to our knowledge of the subject.

Mall's article on the development of the diaphragm and cœlom represents in a large measure his own researches in the subject.

The development of the integument is fully discussed by Felix Pinkus. His article includes the consideration of skin pigmentation, dermal ridges and folds, metamerism of the skin, Mongolian spots, hair whorls, the ontogeny and phylogeny of the hair.

He concludes from the evidence, experimental and otherwise, that the melanin is formed *in situ* in the epidermis. The writer does not believe that the evidence is so conclusive on this point as Pinkus represents.

Perhaps the most elaborate and complete article in the book is the one by Bardeen on the development of the skeleton and connective tissues, occupying some 160 pages. It includes a discussion of the histogenesis of the connective tissues, and morphogenesis of the skeletal system including variations and abnormalities in skeletal development. He divides for consideration the development of the cartilage bones into three stages, the blastemal, chondrogenous and osteogenous. This discussion is based largely on his own work and that of Lewis already published. He opposes Rosenberg's theory of the cephalic shifting of the ilium during ontogeny.

The article by W. H. Lewis on the development of the muscular system is an excellent discussion of the subject and is based largely on his own work. The subjects included are the histogenesis of muscle, the segmentation of the mesoderm and the development of muscles in groups and individually. Contrary to the usual view of anatomists he finds no cephalic myotomes but derives the orbital muscles from a mass of mesoderm on the dorsal side of the optic stalk. Also, he fails to find occipital myotomes but believes that the tongue musculature develops from the mesoderm of the floor of the mouth. Futamura's description of the genesis of the face muscles is followed, deriving them from the hyoid arch.

The illustrations in this volume are numerous, but in some cases they are not so good as such an excellent text deserves. A considerable bibliography is appended to the sub-divisions of each article. No index is furnished.

This country is certainly to be congratulated on the excellent showing made by its anatomists, and Mall in particular is to be felicitated on the excellence of the volume. Anatomy in America is greatly indebted to the work, influence and high ideals of Mall. The second volume will be awaited with great interest.

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Twenty-ninth Year. Price 9/6. (*Bristol: John Wright & Sons, Ltd. New York: E. B. Treat & Co., 1911.*)

This is one of the best books in English covering the progress made in all branches of medicine during the past year. The articles are carefully prepared by physicians thoroughly acquainted with the subjects discussed by them. The majority of the contributors are English, but in the list are also the names of two Americans, one Canadian, two Germans, and a Frenchman. The work is supplied with an excellent table of contents, and many good illustrations. It contains also a valuable addition in a list of the principal medical works, and new editions published during 1910, and another of asylums and a trade directory which makes it of especial use to English practitioners; but for other practitioners as well it is an excellent annual.

Puerperal Infection. By ARNOLD W. W. LEA, M. D., F. R. C. S., Lecturer in Obstetrics and Gynæcology, The University, Manchester, England, etc. Price $9. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

For a long time German monographs upon practical medical subjects have been available, but similar compilations are only beginning to appear in English. There is particular good fortune in having such an excellent one, as is here given, upon puerperal infection, for this is by far the most important complication with which the obstetrician meets.

The author quotes statistics from the British Registrar General's office, which indicate "that one-half of all the deaths of women occurring in connection with child-birth are referable to infection, while its remote results are a source of ill-health to a much larger number." We are shown that there has been only a slight diminution in the mortality from this disease during the past 40 years, and that in some parts of the United Kingdom there is even a tendency toward an increase. The total puerperal death rate was 5.9 per 1000 from 1851 to 1855; it still amounted to 4.2 per thousand between 1901 and 1906. In England and Wales alone from 3000 to 5000 women die annually from this largely preventable complication. Statistics further indicate that the incidence of infection is very much greater in country districts than in the cities where fairly good conditions would seem to prevail. However, the author regards the whole situation as a grave reproach to our times, and in the prevailing conditions he has found sufficient stimulus to prepare this volume of nearly 400 pages.

The monograph views the subject from every side, and in exhaustiveness compares favorably with the article by Von Herff in Von Winckel's Handbuch. It must prove helpful to those who teach obstetrics, but will perhaps have an even greater value for the practitioner. Fully two-thirds of the book is devoted to clinical matters, and one-half of this section deals altogether with treatment. As might be expected, means of prevention are emphasized as the most important feature in combatting infection, but curative measures are discussed at great length and their relative values carefully weighed. The recommendations made are unusually trustworthy. In the discussion of therapeutic measures about which there is some diversity of opinion, the evidence of different advocates is impartially given, yet the author always frankly commits himself to one view; herein he displays clear reasoning and reaches sound conclusions.

The same judicial qualities are apparent in the first portion of the volume which deals with the bacteriological and pathological phases of puerperal infection. The more recent contributions along these lines have been incorporated, and in many instances first hand information relative to disputed points is given. Thus, from his own investigations the author believes that streptococci may occasionally be found in the vagina during pregnancy. He has also observed that such organisms may possess hæmolytic properties.

The pathology is discussed at length, and the suggestions it affords as to treatment are indicated. The author agrees with those who find in the reaction of the endometrium a very good argument against curetting an infected uterus, for this operation usually does no more than remove nature's defense against the disease.

The one criticism which may be fairly offered pertains to the pathological illustrations: these do not reach the standard justified by the text. The book is a valuable addition to the literature of infection, and will be welcome to those who are practising obstetrics.

Urgent Surgery. By Félix Lejars. Professeur Agrégé à la Faculté de Médicine de Paris, etc. Translated from the sixth French edition by William S. Dickie, F. R. C. S., etc. Volume II. Illustrated. (*New York: William Wood & Company, 1910.*)

The second volume of this work is divided into four sections, dealing respectively with the genito-urinary organs, the rectum and anus, the strangulated herniæ, and the extremities. Of the first two of these sections it is perhaps sufficient comment to say that they exemplify the excellent characteristics of the work as a whole. That is, the subject is handled concisely and clearly, yet with no tendency to a restriction to simple generalities, as many quite unusual conditions are discussed and typified by case-reports. Logical subdivision of the subject matter into topics and paragraphs, with typographical arrangements to emphasize headings and important conclusions, aids greatly in dispelling the inevitably forbidding effect of page after page of unvarying print, and renders quick consultation of the book easy. The work is further distinguished from the usual uninspired recitation of common places by the numerous ingenious bits of technique and the wealth of striking clinical observations, which give so strong a note of the writer's personalty and add so much to its practical value.

The part of the book devoted to the urgent surgery of hernia demands more consideration than the above remarks, which are true of the work as a whole. This section really constitutes a monograph of authority, and a masterly treatment of emergency hernial surgery. It is the most comprehensive and rational handling of this highly important phase familiar to the reviewer. The unusual types of strangulation are ably discussed, and a perusal of this book makes one feel far less likely to overlook or mistreat some of these quite obscure cases. The last part of the book, dealing with the extremities, is likewise eminently rational and practical. The various subjects are presented with an attitude of healthy conservatism, of the sort that is not deterred from recourse to seemingly radical measures when such measures are in fact truly conservative.

There are certain points that strike one as noteworthy for the shade of difference presented from the familiar American viewpoint. One misses any reference to the so-called Mayo closure of umbilical herniae in a transverse direction. There is a decided fondness displayed for more or less complicated apparatus in the treatment of fractures. The author categorically condemns the use of gauze in packing abscess cavities, using rubber tubes exclusively. A number of conditions are included that many would give no place to in a work on urgent surgery, such for instance as the open treatment of certain fractures. This, however, is purely a matter of degree, since most surgery, excepting plastic and other types of work where an optimum period is awaited, is urgent in the sense that the sooner it is done the better, even when there is no imperative need of haste.

The book is properly and most admirably illustrated, most of the cuts being original. The translator deserves high appreciation for a rendition into English so pure and idiomatic that no flavor of the original French of the text is perceptible.

Harvey B. Stone.

A Text-Book of Surgical Anatomy. By William Francis Campbell, M. D., Professor of Anatomy at the Long Island College Hospital. Second edition revised. Illustrated. Price, $5.00 net. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

In the preface to this edition the author states "that only such additions have been made and errors corrected as to make the text more complete and exact. Several illustrations have been replaced by others which more accurately elucidate the text." The merits of this work were noted by us (Johns Hopkins Hosp. Bull., Feb., 1909), and its success, as shown in the call for a new edition so soon, is a natural consequence of its qualities which make it valuable to students.

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NOTICE TO BINDER

This Special Tuberculosis Number is part of the July issue, but an extra number. Special attention is called to the three Stereoscopic Views enclosed herewith in an envelope.

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THE STEREOSCOPIC X-RAY EXAMINATION OF THE CHEST WITH ESPECIAL REFERENCE TO THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.

BY

H. Kennon Dunham, M. D., Cincinnati,

Walter W. Boardman, M. D.,

Assistant Physician, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital,

and

Samuel Wolman, M. D.,

Instructor in Medicine, The Johns Hopkins University.

DISCUSSION BY

F. H. Baetjer, M. D., Louis V. Hamman, M. D., and W. S. Thayer, M. D.

PART I.

By H. Kennon Dunham, M. D.

The object of this paper is to call attention to the principles and technique of stereoscopic X-ray examinations, and to describe the alterations in the normal chest shadows, which we believe to be characteristic of pulmonary tuberculosis.

The X-ray, when properly applied, is an instrument of precision for recording differences of density. On the single negative we have of necessity various shadows superimposed. In stereo-rœntgenographs taken with mathematical precision the chest is seen in true perspective, the shadows occupying the same relative position in the image, as the structures which cast the shadows occupy in the chest. This result is obtained by applying the principles of binocular vision. As you will recall "the retinal images of external objects, particularly near objects, are different in the two eyes. Whenever what we may call a right-eyed image of an object is thrown on the right eye and simultaneously, a left-eyed image is thrown on the left eye, whether in nature or by an artifice, we at once perceive depth or solidity in the object." The technical problem then, in stereo-rœntgenography was, first to obtain two

negatives corresponding to the right-eyed and to the left-eyed image respectively, and second, to view simultaneously, by means of some suitable optical device, the right-eyed image with the right eye and the left-eyed image with the left eye.

There are at present several types of apparatus which enable us to obtain the necessary negatives. The common principles in these are, first, a movable carrier for the X-ray tube, and second, a movable carrier for the X-ray plates.

In the movement of the tube there are four details requiring consideration. First, recalling that the X-rays originate at the so-called target of the tube, this target should be moved in a plane parallel to the X-ray plate, in order that the focal distance may be equal in both exposures. Second, between the first and second exposures the target should be moved a distance slightly less than the inter-pupillary distance. Six centimeters has been found satisfactory. Thus every one who has good use of both eyes can see the stereo picture and persons with a greater pupillary distance can estimate, by means of their personal equation, the amount of fore-shortening and allow for it. Third, the target should be moved in a line parallel to rather than across the spine of the patient because this enables us to see around the ribs, thereby obtaining a less obstructed view of the lung fields. Fourth, the target should not be too near the plate. Twenty-five inches is a good working average.

As to the movement of the plates it is merely necessary that the second plate on exposure occupy the position held by the first plate during its exposure. Finally, the total time required for the two exposures, and the movement of tube and plates must not exceed a period of easily sustained inspiration, a time well under ten seconds. For observing the finished plates, the stereoscope devised by Whetstone early in the last century, is most generally used.

Turning now to a study of the shadow pictures seen in stereo-rœntgenographs of human chests, let us first consider the normal before attempting to describe the tuberculous.

On examining a stereo-rœntgenograph of a normal thorax, one sees the shadow picture of the bony framework, with its covering of soft parts, enclosing the chest cavity, except below, where it is bounded by the shadow of the diaphragm. The shadows within the chest cavity, seen as we have stated, in their normal relations, are readily divided into three main groups: first, the "heavy central shadow," extending irregularly from the upper boundary of the chest cavity to the diaphragm; second, the "hilus shadow," radiating irregularly to a distance of four or five centimeters on either side of the fifth, sixth and seventh dorsal vertebræ; and third, the "linear markings" seen in the lung fields.

The "heavy central shadow" need not here be described in detail. It is cast by the vertebræ and the mediastinal contents; the heart, aorta and other large vessels, trachea, oesophagus, lymphatics and connective tissue. The trachea can usually be distinguished as a band of less density bordered by parallel bands of great density, extending downward from the neck. Often it can be seen to divide in front of the fifth dorsal vertebra, the shadow of one bronchus going to the right, and the other to the left hilus. The right is the more often seen as the left passes under the aortic arch and is generally obscured for some distance. In good plates, these bronchial shadows may be seen to subdivide and extend into the lung fields, as a part of the heavy trunks, to be described directly.

The hilus shadow, as has been stated, is cast by the primary branches of the pulmonary vessels with their contained blood, the walls of the primary bronchi, and the lymphatic and fibrous tissue surrounding these structures. Normally, the hilus shadow is of moderate density, irregular in outline and of small extent, merging internally with the heavy central shadow. Externally the hilus has a sharp border which is made irregular by the heavy trunks emerging from it into the lung fields.

The shadows in the lung fields may be subdivided into two groups; the heavy trunks and the fine linear markings: The heavy trunks appear as definite shadows radiating from the hilus shadow toward the periphery. Three groups can usually be seen on the right side, one group running upward and outward, another outward and the third downward and outward. These groups mark what we call divisions. They correspond roughly to the lobes of the lung. On the left side only two such groups can be seen, one extending upward and outward, the other downward and outward. Distally these heavy trunks divide and subdivide producing the radiating shadows designated as the fine linear markings. Examined more carefully, these fine radiating shadows appear as fairly definite straight lines extending toward the periphery, but with our technique, they are lost on the normal plate before they reach the periphery of the lung. These shadows are the combined shadows cast by the blood vessels with their contained blood, the walls of the bronchi, reinforced by the accompanying lymphatics and fibrous tissue. The heavy trunks are the shadows of the large branches distributed to separate lobes of the lung, the linear markings are the shadows cast by the smaller branches distributed to the various lobules of the separate lobes. The linear markings in the lower left division of the lung are rarely distinct, owing to movement, during exposure, occasioned by the cardiac contractions. Therefore alterations in the character of the markings in this region cannot be accurately determined.

Bearing in mind, then, this normal shadow picture, let us consider the stereo-rœntgenographs of chests in which early but definite signs of pulmonary tuberculosis are found on physical examination. In such cases changes are noted in the hilus shadow, the heavy trunks and especially in the linear markings.

The hilus shadow shows usually an irregular increase in area and density with here and there small irregular shadows of very marked density. These bright areas of great density are due to the presence in the chest of calcified caseous or fibrous glands, while the increased area and density of the hilus shadow is due to a general increase in the fibrous and lymphatic tissue which accompanies a local or general mediastinitis. Such changes alone are of very slight diagnostic value as re-

gards the presence of active tuberculosis, since other infections may produce the mediastinal changes and the calcified glands, although probably of tuberculous origin, indicate an old process more or less healed. In fact the presence of calcified glands, the other conditions being favorable, may be taken as a good prognostic sign.

The heavy trunks extending toward the involved area usually appear broader, denser and less regular in outline than in the normal. Here again this change in the heavy trunks is not necessarily tuberculous in origin, so that too great importance must not be attached to this change alone.

Accompanying this alteration in the heavy trunks we find in the diseased area a similar change affecting the fine linear markings. They appear broader, denser and less regular in outline, frequently their course is studded, sometimes almost to obliteration of the lines. We can no longer trace them as radiating but find them broken in continuity and reaching to or near the periphery. As a result of these changes the linear markings appear to cross and interweave, producing a delicate network of varying sized mesh. In the uninvolved areas of the lung the shadow picture may be normal or there may be a slight alteration, such as thickening or increased density of the trunks and linear markings. The anatomical explanation of this altered shadow picture we are not at this time ready to discuss, but we firmly believe that the increase in the hilus shadow, the thickening of the trunks, together with the alterations in the linear markings—increase in density and breadth, studding, interweaving and extension to the periphery—constitute a shadow picture characteristic of early pulmonary tuberculosis. As the lesion progresses the alterations become more marked, the linear markings are more and more broken up and irregular, the studdings become larger and denser and the interweaving closer, until eventually the whole area appears as a more or less homogenous shadow of increased density, due to the presence of gross areas of consolidation within the lung. The more advanced change due to cavity formation we need not discuss at this time.

We have now considered the appearance of the stereo-rœntgenograph of the normal chest and of the typically early tuberculous chest. However, all cases do not fall into these two classes. In the clinical report by Dr. Wolman the cases were divided into five groups: (1) Normal; (2) Diseased but not Tuberculosis; (3) Probably Tuberculosis; (4) Definitely Tuberculosis; (5) Healed Tuberculosis. It must be clearly understood that the stereo-rœntgenographic examination does not draw a sharp line of differentiation between these various groups any more than does the clinical examination. In deciding the border line cases the personal attitude and experience of the examiner is of great importance. We cannot, therefore, set forth any absolute rules to be applied in the classification of every case, but a brief description of the shadow pictures which we consider typical of the various groups may be of some assistance.

The normal picture has already been discussed. It might be mentioned that with advancing age there is an increase in the density of all the shadows, hilus, heavy trunks, and linear markings, for which due allowance must be made.

There are many non-tuberculous pulmonary lesions, but we will not at this time discuss the stereo-rœntgenographic appearance of acute pneumonia, abscess, gangrene, cyst, etc., except to say that they should cause no diagnostic difficulty. There is, however, a large class of cases presenting indefinite clinical signs suggesting pulmonary tuberculosis, which upon examination disclose an interesting and sometimes puzzling appearance. The hilus shadow and heavy trunks are increased in area and density, but sharply defined, radiate, often reaching close to the periphery. These changes are usually diffuse rather than localized and there is also an absence of the interweaving and studding characteristic of the tuberculous cases.

In the probably tuberculous cases some of the characteristic alterations are seen but the picture is not complete. There may be the changes in the shadows cast by the hilus and heavy trunks and suggestive alterations in the linear markings, or some other atypical alteration. These are the cases that require the most careful study and judgment in reaching a diagnosis. The history, symptoms and physical examinations are essential in these cases.

The moderately advanced and advanced cases of pulmonary tuberculosis are readily recognized. In the less advanced cases, careful study will disclose the alterations in the linear markings, heavy trunks and hilus shadow previously described. If in such cases the fine linear markings are fuzzy, or seem to merge to form a cloud effect, such as a film of tobacco smoke in a close room, an active tuberculosis would be suggested.

On the other hand if the linear markings in a limited area are sharply defined and dense and show heavy studdings beyond the trunks, a healed lesion is suggested. This condition is emphasized if it is accompanied with heavy coarse interweavings which reach to or near the periphery. The heavy trunk leading to such an area is usually broad and dense as is the hilus on the same side. Numerous calcified areas would complete the picture, but such a diagnosis should not be made from the plates alone.

One other change which is almost constant in pulmonary tuberculosis, but which is less often diagnosed, either clinically or radiographically, is pleurisy. Marked localized thickenings and interlobular pleurisies are recognizable, but the evenly distributed pleurisy which spreads uniformly over one or both pleural surfaces usually defies detection. On the other hand, pleurisy with effusion, even of moderate magnitude, is readily detected and presents a most interesting appearance in the stereo-rœntgenograph. The fluid is seen to be pressed up around the periphery of the chest cavity. The line of contact between the shadow of the fluid and the shadow of the lung is not, however, a smooth rounded surface, but rather a series of cup-like depressions. Apparently the pressure of the lung upon the fluid is not uniform, there being bands between which the pressure upon the fluid is greater than at the bands. Emerson has compared the position of the pleural effusion pressed upon by the lung with the position of water in a bottle pressed upon by an inflated rubber bag. The simile would be more exact if the rubber bag were covered by a balloon net. Regarding the oft repeated statement that in pleurisy with

effusion the upper border of the fluid moves on change of position of the patient; the X-ray shows but slight if any change in the fluid level whether the patient be in the erect or recumbent position.

The report of Dr. Wolman clearly illustrates the value of this method of studying pulmonary lesions. So far as we know, this is the first report of any careful stereo-rœntgenographic study of the alterations in the fine linear markings occurring in pulmonary disease and the application of this knowledge to the diagnosis of pulmonary tuberculosis. We hope in the near future to be able to explain on anatomical grounds the alterations in the appearance of the linear markings. However, although the method is still empirical and controlled only by careful clinical examinations, we are firmly convinced of its great worth and feel that its more general adoption would greatly increase the value and accuracy of the radiographic diagnosis of pulmonary conditions.

PART II.

By Walter W. Boardman, M. D., and Kennon Dunham, M. D.

There is considerable diversity of opinion as to the value of Rœntgen rays as an aid in the diagnosis of early pulmonary tuberculosis, some authorities placing them above ordinary physical examination, others on a par with physical examination and still others denying to them any such position. To investigate this matter it was decided to install an X-ray apparatus in the laboratory of the Phipps Dispensary and to study an extensive series of cases, controlled by careful clinical examination, tuberculin tests, etc.

In reading an X-ray plate, as in the study of a pathological specimen, it is first necesary to become familiar with the normal before trying to interpret the abnormal. Further, as in studying a pathological specimen it is important to know the structure and arrangement of the various units, so in an X-ray plate it is important to know the anatomical basis for the shadows seen. We therefore turned our attention to a consideration of this subject.

Remembering that in an X-ray plate we have merely a record of differences of density,—the tissues of greater density appearing as light areas, those of less density as dark areas,—we know that the shadows seen correspond to structures in the chest possessing greater density than the structures immediately surrounding them. On the single plate we have of necessity various shadows superimposed one upon the other. In stereoscopic plates, however, the chest is seen in perspective, the shadows occupying the same relative position in the image as the structures which cast these shadows occupy in the chest. The advantage of the stereo-rœntgenogram for the careful study of the various shadows must therefore be self-evident.

Turning then to a consideration of a stereo-rœntgenogram of a normal chest we see the shadow picture of the bony framework, with its covering of soft parts enclosing the chest except inferiorly, where the shadow of the diaphragm is seen. The shadows within the chest cavity seen, as we have stated, in their normal relations, may readily be divided into three main groups: first, the heavy central shadow extending from the upper boundary of the chest cavity to the diaphragm; next the hilus shadows, radiating irregularly to a distance of four or five centimeters on either side of the center of the preceding shadow, and finally the finer markings seen in the lung fields.

Owing to imperfections of apparatus, the hilus shadows and the finer markings were rarely, if ever, seen upon the plates of the earlier workers and it was not until 1900 that they attracted any serious consideration. Thus Hickey[1] states that we find various shadows constantly present which are interpreted as shadows of the bronchi by some, shadows of the pleura by others, and shadows of consolidation by still others. However, he believed them to be perfectly normal, and basing his opinion on various injections, concluded that they were the shadows of the larger pulmonary vesels.

Holzknecht[2] believed that the hilus shadows were due to pulmonary blood vessels; but to the smaller vessels situated near the surface of the chest next the plate, rather than to the large centrally situated vessels.

De la Camp[3] disproved Holzknecht's contention by X-raying serial frontal sections of a cadaver. By this means he definitely proved that the hilus shadows were due to organs which originate at the root of the lung and branch out toward the periphery and are not due to formations near the plate. From various injection experiments he also concluded that the bronchi were responsible for these shadows and that the vessels took practically no part in them.

Holzknecht and Kienböck[4] rejected the conclusions of De la Camp and stated that they believed the pulmonary vessels were primarily responsible for the shadows and that the bronchi participated in them to but a slight extent.

De la Camp,[5] after further careful experimental work, acknowledged that the blood vessels might cast some shadow, but held that they were secondary in importance to the bronchi as a source of the hilus shadows.

Cowl[6] very definitely states that the shadows normally present in the fields of the lungs are due to the ray-like spreading lung vessels and bronchi, but he brings forth no proof of his statement.

Rieder[7] speaks of the irregular spotted markings seen in the lung fields and states that they are caused more by the pulmonary vessels, especially the arteries, than by the bronchi. Later he states that the anatomical nature of the shadow stripes and hilus shadows has not yet been determined, but that most investigators believe both bronchi and blood vessels play a part in the production of these shadows.

Cunnington[8] describes a "tree branch striation" which he noted in only a few of his tuberculous cases and which he believes is due to the distended lymphatics draining the involved areas.

Many others have expressed opinions regarding the anatomical basis of these shadows, but have made no attempt to prove their statements. As Rieder has said, the most generally accepted opinion regarding these shadows is that they

are due to both blood vessels and bronchi. However, in 1910 Fraenkel and Lorcy,[9] after some careful experimental work, conclude that "the anatomical sub-stratum of the hilus shadow consists entirely of the blood vessels of the lungs and that under normal conditions the bronchial arborization gives no shadow on the Röntgen plate. It is, however, quite possible that in abnormal conditions, dilated bronchus filled with pus, it may give a shadow."

From the foregoing references to the literature it is evident that the question as to the anatomical basis for many of the shadows seen in X-ray plates of the chest had not been settled. In our investigations upon this question the work falls into four divisions: first, studies of stereoscopic X-ray plates of normal and diseased chests before death; second, studies of stereoscopic plates taken shortly after death, the X-ray reading being carefully compared with the autopsy findings; third, studies of stereoscopic X-ray plates of animal and human beings in which blood vessels and bronchi had been injected with bismuth or other similar materials; and fourth, studies of stereoscopic X-ray plates of the lungs of animals and human beings upon which more or less dissection had been done. The use of the stereoscope and the dissection were of greatest value.

From our study of the stereoscopic X-rays of normal and diseased chests, several points were settled. First, the hilus shadow is due to structures originating at the root of the lung and radiating toward the periphery, as demonstrated by De la Camp, since with the stereoscope these shadows were seen in their normal relations to the other structures in the chest. Second we were able to divide these radiating shadows in the hilus region and also in the lung fields into groups corresponding to the anatomical division of the lung into lobes; three on the right, two on the left. These subdivisions were very beautifully seen in the stereoscopic plates of injected lungs.

The shadow cast by the heart, with its surrounding pericardium and by the aorta, is too well known to require comment. The tracheal shadow, in many plates, could be definitely traced from the larynx into the hilus shadow as a band of slight density lying between parallel bands of great density; in several cases the divisions and subdivisions could be clearly traced well out into the lung fields. Aneurisms and dilatations of the arch of the aorta were readily recognized and their location determined.

From our autopsy work we satisfied ourselves that enlarged and calcified lymph glands may be easily recognized if occurring about the edge of or outside the heavy central shadow; if they occur within the heavy central shadow it may be impossible to pick them out. Without doubt the heavy central shadow is cast by structures in the mediastinum; the heart with its pericardium and great vessels, the oesophagus, the walls of the trachea, the lymphatic glands and the mediastinal connective tissue. But it is difficult or impossible to recognize the shadows corresponding to some of these different structures.

One of our autopsy experiments gave interesting information concerning the shadow seen along the right side of the vertebral shadow and extending from the clavicle to the base of the heart. This shadow must be cast by structures on the right side of the superior mediastinum. Here we have the superior vena cava surounded by lymphatics and mediastinal tissue. In order to demonstrate what part, if any, this vessel played in the production of this shadow, a body was placed upon the table and a set of plates taken. The right internal jugular vein was then opened and a rubber tube filled with lead shot passed some distance into it and a second set of plates taken. In these the shadow of the tube and shot can be seen extending from the neck through the shadow under consideration and into the heart shadow. At autopsy the tube was found to have traversed the right internal jugular, the right innominate, the superior vena cava, the right auricle and to have entered the inferior vena cava. We therefore feel justified in stating that the superior vena cava, with its contained blood, is at least in part responsible for the shadow seen; the lymphatics and fibrous tissue, however, must play some part in its production.

The results obtained from our injection experiments of animal and human lungs were disappointing. Plates taken after injecting bismuth into the trachea and bronchi showed shadows apparently corresponding in position and size to the shadows normally seen at the hilum and in the lung fields. However, plates taken after similarly injecting the blood vessels disclosed shadows also apparently corresponding in position and size to the normal shadows. If both bronchi and blood vessels were injected the shadows appearing on the plates were too dense to allow of careful study. Hence as a means of settling the disputed question this method was valueless, as might have been inferred by the widely different conclusions reached by the earlier investigators using the method.

Our dissection work on animal lungs was more satisfactory, especially the series in which pigs' lungs were used. These gave very beautiful pictures showing the bronchi as areas of decreased density. Partial injections of pigs' lungs showed the artery to be directly in contact with one side of the bronchus, the vein in contact with the other side. An instructive experiment consisted in carefully separating the lobules from over a bronchus, which was exposed throughout its course from hilum to periphery. A section of the bronchus was now removed and placed on another portion of the lung. The plates taken showed first a definite shadow cast by the removed bronchus; second, definite shadows cast by the artery and the vein in the space from which the bronchus had been removed. These latter shadows were less dense than the shadows with which they were continuous above and below. In other words, the arteries and veins cast shadows in X-ray plates of pigs' lungs, but normally their shadows are augmented by the shadow of the bronchus. Thus the veins, the arteries and the walls of the bronchi cast shadows of great density in the pigs' lungs; the lumen of the bronchi appears as a shadow of slight density. It now became important to repeat this experiment on a human lung.

To this end a normal human lung was obtained as soon

after death as possible, inflated to its natural degree and the first set of plates taken. In these, lines of increased density were readily seen, radiating from the root of the lung toward the periphery. The lung tissue in the region corresponding to one of the more definite lines was carefully separated until a vessel was exposed throughout its course. In the second set of plates the shadow cast by the exposed vessel, a vein, was seen to correspond in position to the shadow on the first plate. The vein was now carefully removed and placed across another portion of the lung, and a third set of plates taken. In these a definite shadow was cast by the removed vein and a shadow was still present in the original position but of lessened density. Beneath the vein lay the artery and this was now removed and placed parallel to the vein, and the course of the bronchus which was now exposed was mapped out with two pins. In the fourth set of plates the bronchial shadow was distinct, although faint, running between the pins, and a definite shadow was present corresponding to the removed artery. The bronchus was now removed and placed parallel to the vein and artery. The plates now showed an absence of any shadow in the original location and definite shadows cast by the vein, artery and bronchus. The proximal end of the bronchus in which cartilage was present cast a very marked shadow. A section of the primary bronchus and of the large thick walled pulmonary artery was now placed side by side on another portion of the lung, and X-ray plates were made. The plates showed a very definite shadow cast by the primary bronchus and a much less marked shadow cast by the walls of the pulmonary artery. Finally two other vessels were exposed and by means of syringes blood, to which a small amount of sodium citrate had been added to prevent coagulation, was injected directly into them. The plates of this last experiment showed slight but definite increase in the density of the shadow beyond the tip of the syringe needles, the site of the injected blood.

We believe that we have proved in this experiment beyond the question of a doubt that the walls of the arteries, the walls of the veins and the walls of the bronchi cast shadows in X-ray plates of normal lungs removed from the body and that these structures bound together as they are by a small amount of fibrous tisue and surrounded by the lymphatics, are collectively responsible for the shadows seen in the parenchyma of the lungs. Furthermore, that the blood normally contained in the pulmonary vessels increases to some degree the density of the shadow cast, and finally, that the walls of the large bronchi are capable of casting very definite shadows which normally are heavier than the shadows cast by the walls of the large vessels. However, the large vessels, with their contained blood, cast a homogenous shadow, whereas the bronchi, with their contained air, cast a very different shadow, consisting of two parallel bands of great density separated by an area of slight density.

We therefore believe that the anatomical basis of the shadows seen in the lung fields and at the hilum in X-ray plates of normal chests is definitely settled. The hilus shadow is caused by the primary branches of the pulmonary vessels with their contained blood and by the walls of the primary branches of the bronchi, together with the lymphatic glands and fibrous tissue which accompany these structures and bind them together. Remembering that the large blood vessels cast a uniform shadow, the blood vessels probably account for a greater part of the hilus shadow than do the two parallel shadows cast by the branches of the bronchi; however, this bronchial shadow is a very definite part of the general whole. The shadows seen in the lung fields are also due to the blood vessels with their contained blood and to the walls of the bronchi. The surrounding fibrous and lymphatic tissue is normally so slight that it probably plays little part in the production of these shadows. Here again the blood vessels, with their contained blood, must cast more shadow than do the walls of the smaller bronchi with their contained air, but it is evident that this bronchial shadow cannot be neglected as a factor in the production of the finer markings in the lung fields.

LITERATURE.

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PART III.

By Samuel Wolman, M. D.

The purpose of this paper will be better accomplished if I confess to you that in the first few days of the work, I conceived a profound distrust of diagnoses that had to be based on Dr. Dunham's peculiar stereoscopic markings. But now I can testify to my conversion to a belief in these same scorned markings. The original distrust was as natural as the consequent conversion, for the markings and interweavings declared to be pathognomonic of tuberculous changes in the lung tissue, had no assignable anatomical or even clinical basis. We had all read of tubercles large and small, of caseated areas, of foci of softening, of thickening and congestion around all such areas, even of gross tuberculous fibrosis, yet nothing of all this was competent to explain why, for example, in the presence of a small tuberculous focus at an apex, a peculiar characteristic, recognizable, and yet delicate tracery should develop throughout a large surrounding area, and extend to the very periphery of the organ; and the more advanced the lesion the more extensive, the grosser this tracery. These markings being unexplained, mysterious, not attachable to our existing system of knowledge, had then for us no meaning. Nor even now do we know of any acceptable explanation. However, after sub-

jecting these markings to a severe clinical criticism, we can state that undeniably they possess empirical truth.

The clinical notes of all the cases reported in this paper, were made before the radiographs were taken. The radiographic study and diagnosis, on the other hand, were made without any knowledge of the history or clinical findings. Needless to say, the appearance of the patients themselves was not such that snap-shot diagnoses could be made by the radiographer, for we did not send Dr. Dunham emaciated and buxom patients alternately for examination. Indeed, in order to make the test severe, we sent comparatively few advanced cases, since the plates of these showed gross markings, such as are easily seen on single plates, and it was the stereographic markings that we were most curious to study. And then too, our study of the advanced cases soon convinced us that our clinical technique could be safely subjected to a more searching criticism, for there was an extremely gratifying coincidence of the physical and radiographic findings. And here it may be well to emphasize that the stereographic plates show not less, but more, than the single plate readings, so that not only were we testing the radiograph, but the radiograph, in turn, was testing the clinical work.

In recording the clinical findings, our aim was first to note every abnormality of the physical signs; secondly, on the basis of history, symptoms, sputum examination, tuberculin tests, and physical signs, to decide whether these signs should be attributed to tuberculosis or not. The radiographer, in his turn, noted all abnormal markings in the lungs, and would then commit himself in writing as to their etiology.

This series embraces 92 cases, and in only seven of the 92 was there a disagreement between the clinical and the X-ray findings. However, in six of these seven, the disagreement was only partial and comparatively slight, so that in only one of the 92 cases was there a definite clash.

Let us first study the six instances of only partial agreement:

Case I.—Clinically, impairment at right apex. The stereoscope shows impairment at both apices, but much more marked at the right. Both clinical and X-ray diagnoses are: not definitely tuberculous.

Case II.—Age 5. Clinically, transient râles in the upper chest on each side, which we were not willing to diagnose as tuberculous. The X-ray suggests tuberculosis in both upper lobes. The 1 per cent tuberculin eye test was positive.

Case III.—A girl of 16 with mild mitral insufficiency. Clinically, fibrous changes in right upper and lower lobes, with a definite consolidation at the left base. This girl had but few symptoms, except some weakness, and a moderate cough. She was examined by Dr. W. S. Thayer. The question arose as to whether the insufficiency could explain the lung signs. The X-ray showed the changes discovered in the right chest to be of a tuberculous nature. The consolidation at the left base was not shown, but Dr. Dunham admits difficulty in reading the left base, especially where the heart is enlarged.

Case IV.—Clinically diagnosed as tuberculous at the right apex. The X-ray diagnoses lesions at both apices, but more marked on the right side.

Case V.—Clinical diagnosis; marked involvement of the right lung. On the left, a large area of hyperresonance with a few crackles. The X-ray agrees as to the right lung, but shows also a large lesion in the left. (This may have been concealed, however, by the compensatory emphysema noted clinically).

Case VI.—Colored woman. Wasserman test +, eye test ++ (5 per cent). Clinically, only an impaired note over both upper lobes, which we were chary of diagnosing as tuberculous on account of the lues. X-ray diagnosis, tuberculosis in both upper lobes.

Case VII.—The one of disagreement—concerns a child of three years. The skin-test was positive; otherwise the examination was clinically negative, but the X-ray showed a small lesion in the left lung.

These seven cases comprise our entire list of differences, and we feel that neither the clinician nor the radiographer emerges badly wounded. Hereafter our talk is of harmony, and as follows.

The next group is of 38 cases, in which, clinically, the diagnosis of pulmonary tuberculosis was made definitely. Twelve of these are far advanced cases, and in 16 tubercle bacilli were found. In all these 38, there was agreement between the clinical findings and the plates, as to the position, grade, and general extent of the lesions. (But it must be said that in every case, the pulmonary disturbance, as judged by the interweaving, is more extensive than the lesion, as judged by clinical means. Even a slight apical lesion appears as a long track from the root). Four of the cases were clinically stated to be fibroid. The same diagnosis was made by the X-ray. However, two cases which had at one time given definite physical signs, and had now been for some time without symptoms, and almost without signs, were reported by the radiographer as tuberculous, without any saving note. And here we must state that the X-ray, even with the stereoscope, does not seem to be able to differentiate active from healed lesions. However, neither do the physical signs.

We then have 24 cases in which definite physical signs were found. For these signs a tuberculous basis was suspected, but could not be definitely affirmed, clinically. In all these 24, the X-ray showed abnormalities corresponding to the physical signs, and in 12 of the 24, a diagnosis of tuberculosis was made. It is extremely interesting to find that in 12 of these cases, that is, in 50 per cent of those marked only probably tuberculous, clinically, the radiographer too, made a diagnosis of probable, rather than positive, tuberculosis. This conservatism on the part of the stereograph, was extremely reassuring to those of us who were timid about relying on the mysterious interweavings. Case VI of this series had a mitral lesion, which made us hesitate in diagnosing tuberculosis. The X-ray said tuberculosis, and the sputum showed tubercle bacilli. However, Case VIII, which the X-ray diagnosed as only probable, we fully believe is tuberculous, on the basis of later signs and symptoms.

Case XIV is one of general bronchitis, with indefinite signs at the apices, but severe constitutional symptoms. Although clinically, we were not ready to diagnose the case as tuberculous, yet we were strongly tempted to do so. However, the

X-ray note made was "borderline case. Suggests thickened bronchi." Later events showed no ground to suspect tuberculosis.

In Case XIX, the clinical diagnosis was, thickened pleura, bilateral. The X-ray note was, "Pleurisy at the apices. Probably an old tuberculous lesion."

In Case XXII, the clinical finding was impairment at both apices, but more on the left. No râles. The X-ray reports both apices involved, but the older lesion on the left.

The next group comprises 14 cases. In these 14, neither the X-ray nor the physical examination noted any abnormalities. It should be remembered that in the entire series of 92, there was only one other case in which the chest was physically negative, and in that case, as already stated, the X-ray showed a lesion. This accord as to absolutely negative findings on both sides of the investigation in 14 out of 15 cases, so reported clinically, is of considerable significance.

The last group comprises eight cases. In these eight, the diagnosis of "not tuberculous" was made by both methods, but in contrast to the preceding group, physical signs were present, and were similarly reported by the radiographer, and by the clinician. It should here be noted that evidently the stereograph does not report all abnormalities in the pulmonary parenchyma as tuberculous. (This indeed appeared also in the group of probable cases, as noted above). Case I of this series had definite tertiary lues elsewhere in the body. Case II was one of bronchial asthma. The X-ray reports signs in all five lobes, but they suggest bronchial trouble, rather than tuberculosis. The patient, at the time the picture was taken, did not give evidence of having secretion in the bronchi. The lungs that day seemed clear. In this case, too, pleural thickening over the right upper lobe was diagnosed by both methods. In Case III, Dr. Dunham refused to make a diagnosis, but said the plate showed what was perhaps a healed lesion. The clinical history, too, suggests an old infection, whatever the etiology.

We wish further to mention two cases. Both were young adults, both in apparently good health, but each had a history of chronic cough and expectoration. Physically, there were signs of severe general bronchitis. However, in each case the râles were more numerous on the right side, and there was moderate impairment over the upper lobe of the right lung. The stereograph diagnosed tuberculosis in both cases, more marked in the right lung. The patients, however, seemed in good health, and we might have been skeptical, had not one of them produced tubercle bacilli in the sputum. And we are inclined to believe the diagnosis in the other case, too, since the signs are more emphasized on one side.

To sum up: In only one of the 92 cases was there an entire disagreement; in only six, a partial disagreement. In 85, there was entire agreement. Of these, 39 are positive clinically, 24 are probably clinically, and 12 of these 24 are diagnosed as only probable by the X-ray. In eight cases, physical signs were found by both methods, but they were diagnosed as not tuberculous, and in 14 cases, there was an agreement as to the entire freedom of both lungs from abnormalities.

We think these figures rather convincing as to the ability of the stereograph to discover abnormalities and to diagnose them; and although in the great bulk of cases, it tells us no more than a careful clinical examination, yet in a fair number of cases, and these among the most interesting and puzzling, it gives additional information. But we must add the caution that a careful history is indispensable, since not even the stereograph can tell an active from a healed lesion.

Discussion.

Dr. F. H. Baetjer.—I have listened with a great deal of pleasure to these three papers and must congratulate the authors on the admirable work they have presented to us tonight.

Dr. Boardman's paper was of great interest to me as I think that he has definitely settled the question as to the meaning of the linear radiation that we see in the X-ray plate of the lungs. As you have been told various theories were held as to the meaning of these lines, some looking upon them as simply being the small bronchi, others as being due to the veins and still others as being due to the arteries. I think that he has shown positively that these lines are due to all three. Dr. Dunham's paper was of special interest to me in that I do not agree with him absolutely as to the interpretation of the linear markings. According to his classification the lung is divided into three zones, first, the markings just outside of the sternum, and these he calls the hilum shadows; second, the prolongation of these shadows out a little beyond the middle of the lungs, and third, the zone that is made up of the linear markings extending to the periphery of the lungs. It is especially with the third zone that we have to deal as it is upon these markings that Dr. Dunham makes his diagnosis of early tuberculosis. These lines are not normally present and he has found that when they are present and extend to the periphery it is due to a tuberculous change. As he himself says this method of diagnosis is empirical and has no pathological basis but that his findings have also been substantiated by the clinical findings. Now it seems to me that this is the point where error could so easily creep in. In the first place the only check upon X-ray findings is the clinical findings and it seems to me that this is not an absolute proof. Secondly, it seems to me that any chronic infection of the lungs could just as easily produce changes in the bands which carry the artery, vein and bronchus. In emphysema and chronic bronchitis we see a marked thickening of these bands extending throughout the lungs. I agree with Dr. Dunham that the irregularities along these linear markings which he has termed "fuzzy" are collections of small tubercles but they are seen in a later stage of the disease. Since the X-ray will give us the slightest changes in density the X-ray plate will naturally record very fine and minute changes. In many of the plates these linear markings are very fine and it seems to me that it is impossible for the clinician either by percussion or auscultation to detect them. Our own experience here in the hospital has been that the radiograph will invariably show greater changes than the clinical findings. Consequently in these very early cases where

the clinical diagnosis agrees with the X-ray we are forced to conclude that either the radiographs do not show all the changes in the lung substance or that the auscultation and percussion have reached a degree of surprising accuracy.

Dr. Dunham deserves a great deal of credit for this piece of work but at the same time my feeling is that we must have pathological instead of clinical substantiation before we can absolutely accept this method for the determination of very early tuberculosis.

DR. L. V. HAMMAN.—Dr. Baetjer has discussed these papers from the technical standpoint and perhaps it would be well to say a few words about the early diagnosis of pulmonary tuberculosis from a clinical standpoint. During the six years that the Phipps Dispensary has been in existence we have given more study to this particular question than to any other and the change that has gradually come about in our attitude towards it has been a matter of surprise and of the keenest interest to us. When the dispensary was started those of us who worked there had the average training and skill that comes from some years of medical service in hospital and dispensary. This we considered sufficient for our needs, but from constant and continuous application to pulmonary diagnosis we soon developed a skill that made apparent abnormal physical signs that had previously been overlooked. This was the period of greatest satisfaction and confidence for the signs meant trouble in the lungs and trouble in the lungs spelt tuberculosis and pulmonary tuberculosis needed energetic treatment and such treatment was followed by improvement. We had innumerable cases of early pulmonary trouble in those days, many more than you could find in our records now. We were further intrenched in our confidence by the confirmatory evidence lent by tuberculin. To give added assurance we administered tuberculin to these patients subcutaneously. Of about 36 patients so tested at Eudowood all but one reacted. Slight physical signs and the tuberculin reaction played so smoothly into one another's hands that we at last became suspicious and began to give tuberculin indiscriminately to as many patients as we could control and to our dismay found that about 60 per cent of all individuals react, whether they are suspected of having tuberculosis or not. The advent of the local tuberculin tests allowed us to apply tuberculin on a large scale and to verify our previous observations by convincing numbers. This was the check that made us review more cautiously our previous conviction and led to a less ready and more difficult judgment of our cases. Individuals that formerly would have been peremptorily condemned were now kept under observation instead of being rushed to a sanatorium, and somewhat to our disappointment, they continued well under ordinary conditions of life in spite of the persistence of the abnormal physical signs.

This has brought us to the period where we now are in which the clinical symptoms play such an important rôle in distinguishing active from inactive lesions—of course I cannot go into details.

Some weeks ago a prominent man from the medical clinic came into the Phipps Dispensary to see a patient and casually remarked "of course the patient has tuberculosis." He was told no we really thought the man did not have tuberculosis, when with assumed surprise he replied "why I had no idea that you ever failed to find tuberculosis in a patient." This was to us a very painful display of lack of knowledge of our aims and methods. However, some days later, speaking to a physician extremely active in tuberculosis work, I mentioned that we had grown more conservative in the diagnosis of early pulmonary tuberculosis and he rebuked me with "yes, I know you have, and even too conservative."

The dispensary then is in a not very enviable position—too hot for medical men and too cold for the specialists. In the predicament the X-ray comes in and offers a helping hand.

The result of the valuable work that Drs. Dunham, Wolman and Boardman have done that interests me most, probably because it brings a ray of comforting reassurance, is the remarkable correspondence between the results of the physical examination and the plate readings. Here is at least something definite that we can hang too. A skillful physical examination—and I emphasize skillful—outlines for us with unexpected precision even slight changes in the lungs. The interpretation of these changes may be and indeed is an occasion of keen discussion. With the objective verification it can no longer be insinuated that the signs are the expression of an imagination stimulated to overwork by a prurient enthusiasm, nor that even such minor changes come within the range of normal variation.

There are three points in the X-ray work that particularly deserve emphasis.

1. The lesion in all cases is more extensive than the physical signs indicate. We have already learned this from autopsies and especially from focal tuberculin reactions and have become accustomed to visualize further than a strict interpretation of the physical signs would permit.

2. While in all of our early cases we discover the earliest signs at the apices the X-ray plates show the most marked changes at or near the hilus and bands radiating from here to the apices. This is hardly in accord with anatomical findings and I would ask Dr. Dunham if he can tell us what is the pathological basis of these dense radiating bands.

3. And most important of all I would say that interpretation of these stereoscopic plates is as expert a bit of skill as the physical examination. It is certainly no reflection upon Dr. Dunham's work when I confess that I am unable to see in the plates all that Dr. Dunham sees there. From plate readings alone Dr. Dunham will diagnose one case definitely pulmonary tuberculosis, and another as suspicious. From physical examination alone we are unable to do this. We turn back and rely on the clinical symptoms to decide whether the lesion is an active or inactive one.

DR. W. S. THAYER.—I have been considerably impressed during the last year or so with the real value of the radiograms of the chest in suspected tuberculosis.

The diagnosis of an early or later pulmonary tuberculosis

is often made only by the gathering together and the carefully weighing of a variety of special observations and the results of a radiographic examination are not infrequently of great importance in leading one to the correct conclusion.

The remarkable agreement between the results of physical examination and the radiogram in the cases reported this evening are extremely satisfactory and encouraging. They go to show how much can be made out by a true, careful physical examination.

The wonderful stereoscopic pictures which Dr. Dunham has been able to show us, mark a real step forward in our methods of thoracic investigation.

PAROXYSMAL HEMOGLOBINURIA:
BLOOD STUDIES IN THREE CASES.

By W. L. Moss, M. D.,

Associate in Medicine, Johns Hopkins University.

(*From the Research Laboratory, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital.*)

The studies herein reported have been directed toward the phenomena which the blood of this interesting condition presents, rather than to the clinical features of the disease.

The condition was separated as a clinical entity long ago and the symptom complex sufficiently well known to render diagnosis certain and easy.

From the first recognition of the disease, investigators have busied themselves with the search for an explanation of the remarkable manifestations of the attacks and numerous theories have been advanced to account for them which now have only an historical interest and need not be reviewed, since this already has been done adequately by Eason.[1]

Our present views on the mechanism of the blood destruction during the attacks in this disease date from the publication of Donath and Landsteiner,[2] who showed that hemolysis of the blood of hemoglobinuric patients took place in vitro if the temperature was considerably lowered and then raised.

It had already been suggested, especally by Eason, that the hemolysis in these cases was due to a complex hemolysin of amboceptor-complement nature, whose action bore some relation to temperature, but the proof of the amboceptor-complement nature of the hemolysin, as well as the explanation of the part played by cold, seems not to have been furnished before the work of Donath and Landsteiner just cited.

The fundamental facts brought out by them were as follows:

1. To show the relation of temperature to hemolysis.

Blood from hemoglobinuric patients taken in potassium oxalate solution, to prevent clotting, underwent no hemolysis if kept either at low temperature or at body temperature, but hemolysis occurred if the temperature was first lowered and then raised. The same result followed if a mixture of serum and washed corpuscles from a hemoglobinuric patient was used instead of oxalated blood.

2. To show the amboceptor-complement nature of the hemolysin.

Heating the oxalated plasma to 45° C. for 15 minutes definitely lowered its hemolytic strength, while heating it to 55° C. for 15 minutes destroyed the same.

Corpuscles chilled in oxalated plasma and then removed by centrifugalization did not undergo hemolysis on the addition of normal salt solution or of inactivated hemoglobinuric serum at thermostat temperature, but were promptly dissolved after the addition of fresh normal serum.

On the above evidence the authors convinced themselves of the amboceptor-complement nature of the hemolysin and concluded that the serum of paroxysmal hemoglobinuric patients contains a hemolytic amboceptor which requires for its union with the red blood cell a low temperature, while the union of complement and consequent solution of the cell takes place only at higher temperatures.

While it is true that they bring forth some further experimental evidence in support of this view, it is perhaps significant in the light of the findings of Hoover and Stone,[3] and of my own results to be reported presently, that Donath and Landsteiner do not mention in their first communication having made any attempts to reactivate hemoglobinuric serum heated to 56° C. by the addition of fresh normal serum.

In a later publication[4] they do report successful reactivation experiments but it is to be noted that the reactivating serum (complement) was added to the mixture of inactivated patient's serum and corpuscles before the mixture was subjected to a low temperature and that their reactivation experiments failed if the hemoglobinuric serum was inactivated by subjecting it to a higher temperature than 48° – 50° C. for 20 minutes.

Hoover and Stone made very complete studies on two cases of paroxysmal hemoglobinuria in which they confirm Donath and Landsteiner's conclusions concerning the relation of cold to hemolysis and the amboceptor-complement nature of the hemolysin, as indeed most investigators subsequent to Donath and Landsteiner have done. In opposition to the views of other workers, however, they maintain that, not only does the amboceptor, but also the complement, require a low temperature for its union, the lytic action of the complement, however, only taking place after the temperature is elevated.

Their views and the experiments upon which they are based are best given by a direct quotation from their report.

"0.5 cc. of inactivated H. S. + washed R. B. C. + 5° C. for 30 minutes + 37° C. for one hour.

Now if the normal serum be added and the mixture is placed in the thermostat for many hours, no hemolysis follows.

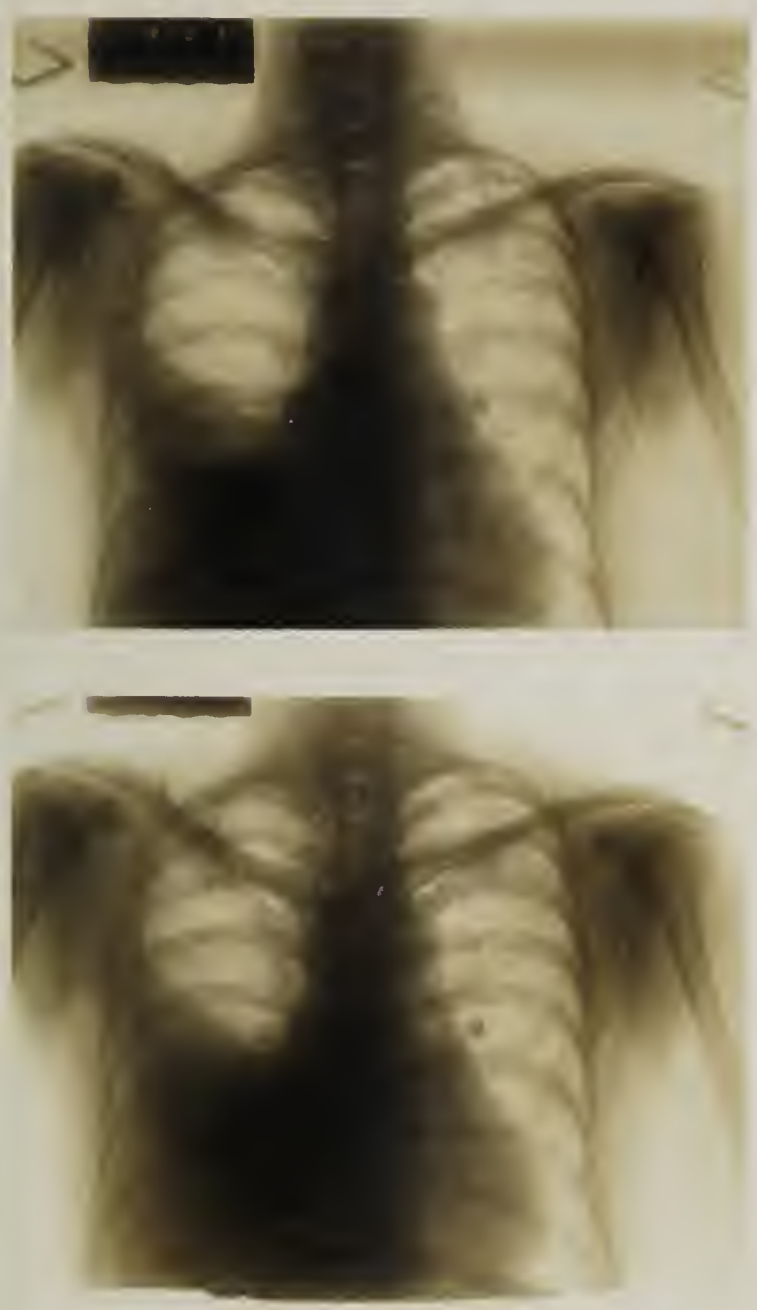

PLATE A.

LEGEND—SEE BACK.

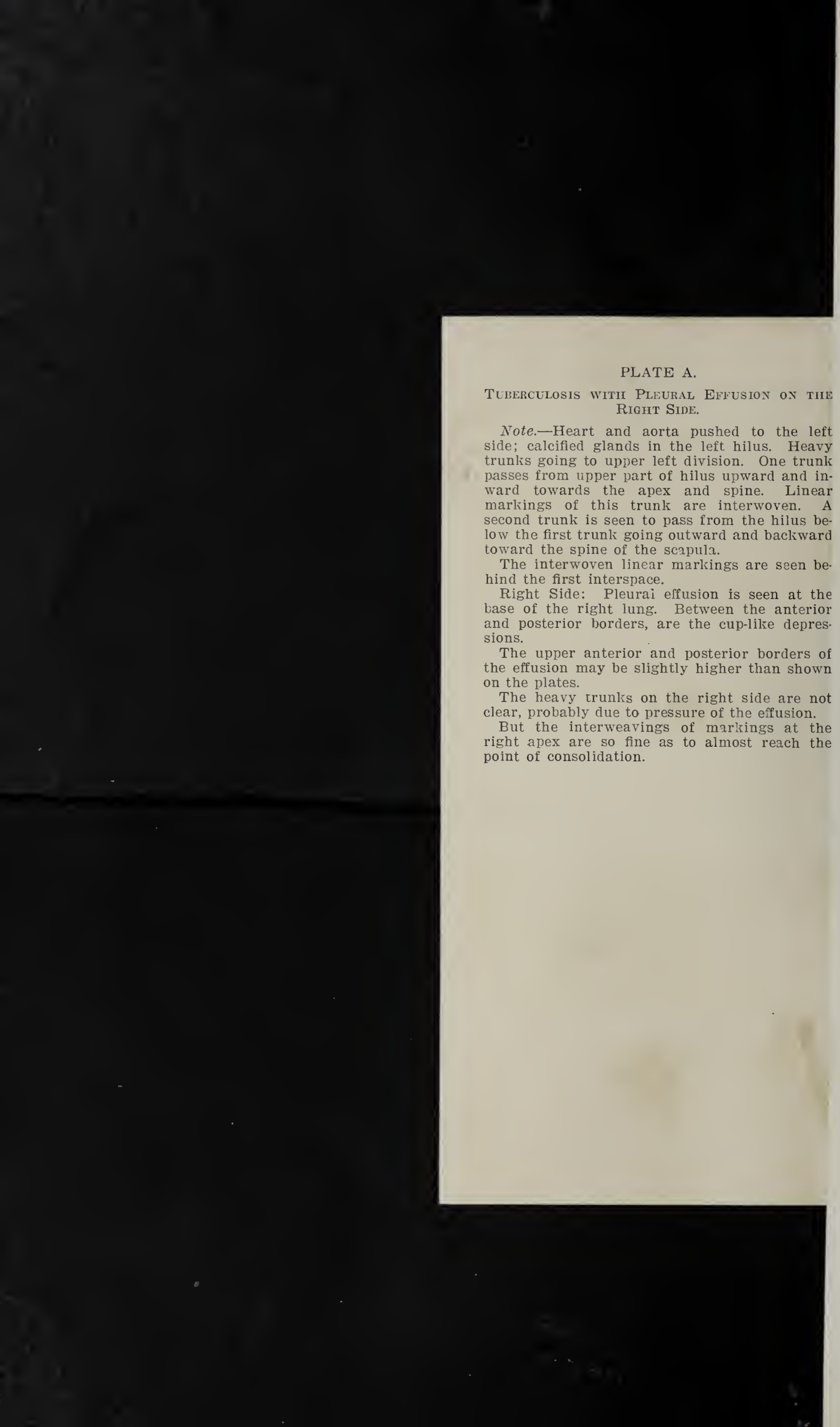

PLATE A.

TUBERCULOSIS WITH PLEURAL EFFUSION ON THE RIGHT SIDE.

Note.—Heart and aorta pushed to the left side; calcified glands in the left hilus. Heavy trunks going to upper left division. One trunk passes from upper part of hilus upward and inward towards the apex and spine. Linear markings of this trunk are interwoven. A second trunk is seen to pass from the hilus below the first trunk going outward and backward toward the spine of the scapula.

The interwoven linear markings are seen behind the first interspace.

Right Side: Pleural effusion is seen at the base of the right lung. Between the anterior and posterior borders, are the cup-like depressions.

The upper anterior and posterior borders of the effusion may be slightly higher than shown on the plates.

The heavy trunks on the right side are not clear, probably due to pressure of the effusion.

But the interweavings of markings at the right apex are so fine as to almost reach the point of consolidation.

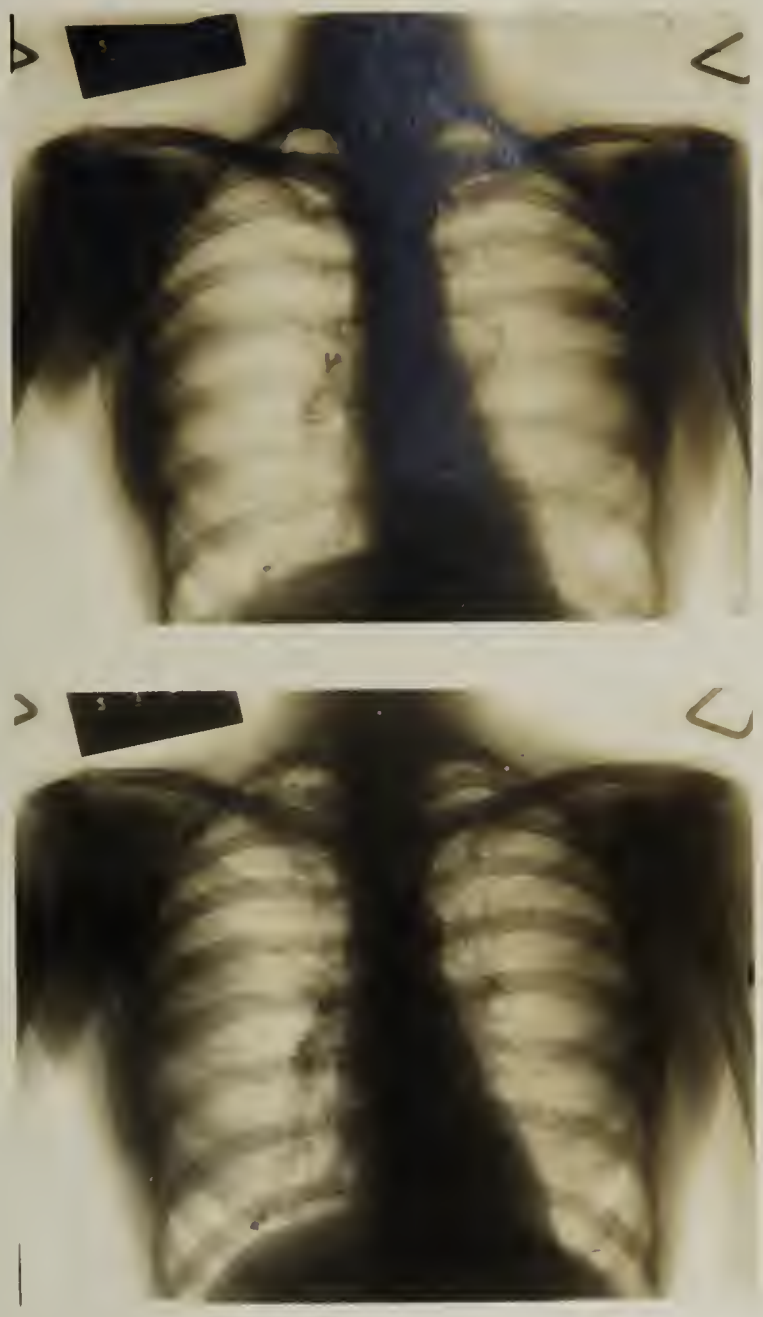

PLATE B.

LEGEND—SEE BACK.

PLATE B.

Pulmonary Tuberculosis.

Note.—Calcification of cartilage of first rib and calcification of the 5th and 6th costal cartilages of the right side.

Calcified areas seen at right hilus and at the base of right lung.

Abnormal shadow is seen posterior to the heart, passing down behind the diaphragm on the left side.

Thickened pleura is noted at the right apex. The lung markings are much disturbed by an innumerable number of fine studdings, and many coarse ones.

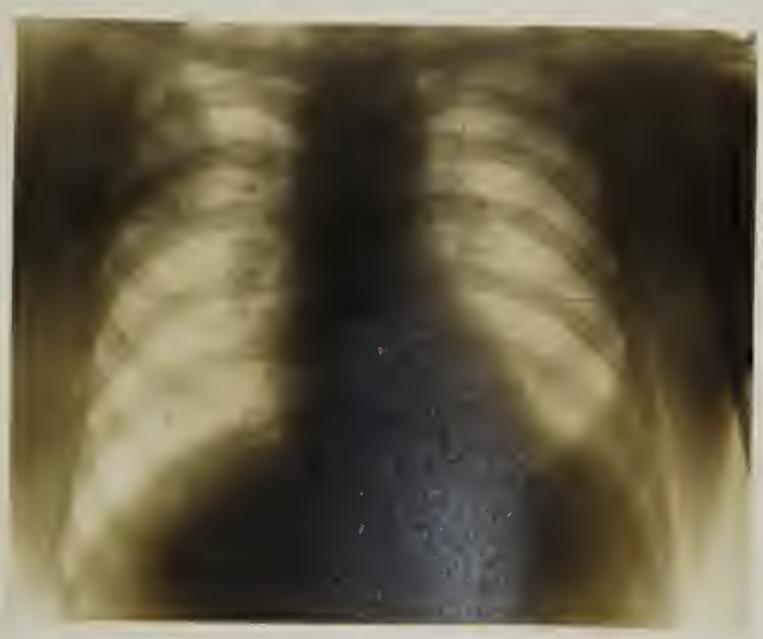

PLATE C.

LEGEND—SEE BACK.

PLATE C.

PULMONARY TUBERCULOSIS WITH SLIGHT EFFUSION AT THE BASE OF THE LEFT LUNG.

Hilus shadows are heavy on both sides, containing numerous calcified areas and one bright area, seen at the posterior base of the right lung, in front of the 9th interspace.

Left apex suggests infiltration as low as the third rib; linear markings are blotted out. On the right side behind the second and upper part of the third interspace, is a dark shadow, which has a heavy trunk passing into it from the right hilus. This suggests a possible tubercular broncho-pneumonia.

Inasmuch as a low temperature was required to procure fixation of the amboceptor to the red blood cell it seemed probable that reactivation experiments had hitherto failed because a low temperature was not employed in fixing the complementophilic end of the amboceptor to the haptophore of the complement. The following reactivation experiment proved successful.

0.5 cc. inactivated H. S. + washed R. B. C. + 0.25 cc. of normal serum + 5° C. for 15 minutes.

The mixture was then warmed to 37° C. and hemolysis followed immediately.

Thus it is apparent that cold is essential for the fixation of both the cytophilic and the complementophilic ends of the amboceptor."

While I have repeatedly confirmed the results of the above experiments, I differ with Hoover and Stone as to their interpretation and will return to this discussion presently.

Meyer and Emmerich[5] have made very exhaustive clinical, hematological and serological studies of four cases of paroxysmal hemoglobinuria.

Reference need not be made here to their observations on the blood pressure during the paroxysms, the leucocytic changes, the appearance of the derivatives of hemoglobin in the urine after attacks, nor to the very interesting clinical observations of these authors, since the present paper does not deal with these phases of the disease.

Meyer and Emmerich report that the blood of their patients did not always show hemolysis when subjected to a low temperature followed by high temperature, as described by Donath and Landsteiner. Thus with their first patient they obtained positive results only 13 times out of 40 tests performed at intervals during five months. Similarly the test often failed to give hemolysis with their other three patients.

The negative results are ascribed in most instances to lack of complement since they found that positive results were obtained much more frequently if normal serum (complement) was added to the mixture of patient's serum and red blood cells.

They found that the complement deficit usually occurred shortly after an attack of hemoglobinuria and ascribed it to the using up of complement during the attack; although they consider that the complement content of the blood undergoes wide variation independently of attacks of hemoglobinuria.

It is interesting that the authors found this deficit of complement did not protect the patients from attacks of hemoglobinuria, for they observed that at a time when the serum could be shown to contain no complement the patient might undergo a spontaneous or induced attack; this paradoxical result they explain on the assumption that complement is formed locally in the surface of the body exposed to the action of cold.

With reference to the union of the red blood cell and amboceptor, Meyer and Emmerich state that it makes no difference whether the complement is added to the mixture of red blood cells and inactivated hemoglobinuric serum before or [illegible]ling the mixture, hemolysis taking place equally well [illegible] r case.

[illegible]cial attention is directed to this point since it stands in [illegible]tion to the results of Hoover and Stone and myself.

Meyer and Emmerich, in summing up the results of their experiments, report that "the amboceptor becomes bound to the blood corpuscle in the cold, but is easily dissociated from the corpuscle at high temperatures." They believe that some of the contradictory reports in the literature are to be explained on this basis. Referring to the work of Hoover and Stone, they say, "While we have seen above, that the binding of the amboceptors to the corpuscles follows in the cold without the presence of complement Hoover and Stone report that the mixture must be cooled in the presence of complement. This appearance is readily explained by the easy dissociability of the amboceptor."

Hoover and Stone do not make the point that the union of red blood cell and amboceptor can take place only at low temperatures in the presence of complement, but that a low temperature is necessary for the union of complement to the corpuscle-amboceptor combination.

There is one paragraph in Hoover and Stone's report which seems to justify the meaning which Meyer and Emmerich ascribe to them, but their further experiments indicate that they did not believe that the presence of complement was necessary for the union between corpuscle and amboceptor to take place, as evidenced by the following quotation from their paper:

"Thus we have shown that if in two stages, 10 drops of a 10 per cent suspension of red cells be added to (1 cc.) the serum and exposed to cold for one hour each time, the amboceptor can be exhausted from the inactivated hemoglobinuric serum."

Furthermore, Hoover and Stone in a personal communication to me stated that they did not hold that the presence of complement was necessary in order that union take place between corpuscle and amboceptor.

With reference to the resistance of the red blood cells of hemoglobinuric patients, Meyer and Emmerich carried out experiments to show that the resistance to certain destructive agents, such as saponin, was greater if the corpuscles had anchored amboceptor than if they were amboceptor-free and therefore they conclude that it is necessary to use amboceptor-free corpuscles in resistance tests. They state that corpuscles from hemoglobinuric patients are less resistant to temperature changes, mechanical influences, dilute acids, and saponin solutions, but that they do not differ from normal corpuscles in their resistance to anisotonic salt solutions.

No attempt has been made to give a complete review of the literature on paroxysmal hemoglobinuria, or even to bring out all the facts which have been established concerning it. Reference has been confined largely to those phases of the subject with which my own work has dealt.

CASE REPORTS.*

CASE I.—G. C., female, colored, aged eight years.

First Admission to hospital, February 9, 1910.

Diagnosis.—Paroxysmal Hemoglobinuria, Congenital Syphilis.

Complaint.—Blood in urine.

Family History.—Father and mother natives of British Guiana, South America. Father alive and well. Mother alive, subject to

* For the privilege of studying and reporting Cases I and II, I am indebted to Dr. S. Amberg, who kindly referred them to me

asthmatic attacks, menstrual periods characterized by profuse sanguinous discharge and each child-birth has been accompanied by troublesome hemorrhage.

The first child, a male, was born in British Guiana 14 years ago, and died at the age of nine years of diphtheria, followed by pneumonia. This child was subject to epistaxis, but withstood exposure to cold well.

Second child, female, died a few days after birth of umbilical hemorrhage.

The third child, female, died at the age of one month from umbilical hemorrhage. Bleeding from umbilicus began 12 hours after birth and recurred twice during the month the child lived.

Fourth child (G. C., the present patient), was born eight years ago in Washington, D. C.

Fifth child, male, alive and well.

Sixth child, still-born.

Past History.—Patient suffered from a vaginal hemorrhage shortly after birth. Measles at three years, chicken-pox and diphtheria at four years, typhoid fever at five years, whooping cough at six years. Has had several attacks of tonsillitis, the last being in November, 1908.

Present Illness.—Began five years ago, when it was noticed that exposure to severe cold would be followed in a few hours by a chill and later by fever and the passage of "bloody urine." The elimination of "blood" in the urine has never persisted more than 24 hours after the onset of an attack. Attacks have never occurred during warm weather; they have been most frequent in the spring and fall of the year, especially in cold, damp weather. The patient's mother states that prior to the onset of the present illness, five years ago, exposure to cold frequently caused a profuse eruption of hives over the face and body, but that since the onset of the attacks of hemoglobinuria the patient has never suffered from hives.

The patient suffered an attack on the day before admission to the hospital and another on the morning of admission.

Physical Examination.—A well nourished child, rather small for her age. Pupils widely dilated, react normally. Breathes through mouth, tonsils greatly hypertrophied, rather pale and contain deep crypts. Teeth normal. Considerable exophthalmos, von Graefe's sign positive, thyroid not enlarged.

Lungs.—Clear on percussion and auscultation.

Heart.—Not enlarged, sounds clear except for a slight systolic murmur at apex, which is transmitted but a short distance into axilla.

Liver.—Somewhat enlarged and readily palpable 2 cm. below costal margin in mamillary line. Spleen is hard and is just palpable at costal margin.

Patellar reflex exaggerated, plantar reflex normal, no ankle clonus.

Cervical, axillary, inguinal and epitrochlear lymph glands markedly enlarged.

Urine on admission was of a dark red, smoky color. Sp. Gr. 1015, faintly acid, contained no sugar, much albumin, and gave a positive guiac test for blood. Microscopically a few white blood cells were seen, but no red cells or casts. Subsequent examinations of the urine during the patient's stay in the hospital revealed no abnormality. The temperature on admission was 99.8° F., but fell to normal within a few hours and remained normal.

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from the Pediatric Dispensary of the Johns Hopkins Hospital, and to Dr. L. F. Barker, who subsequently admitted the cases to his service in the Johns Hopkins Hospital and permitted these studies to be carried out.

For the privilege of studying Case III, I am indebted to Drs. Hoover and Stone, this being one of the two cases reported by them.

Blood Examination.—Fresh specimen showed no poikilocytosis or anisocytosis, no parasites seen.

R. B. C.	4,000,000
W. B. C.	22,000
Hb.	70%

Wassermann reaction positive.

Patient discharged February 23, 1910.

Second admission to hospital, November 10, 1910.

Patient passed through the summer months without attacks, but with the onset of cold weather in the autumn the attacks began to recur.

Wassermann reaction still positive.

Differential blood count on admission:

Polymorphonuclear neutrophiles	50%
Polymorphonuclear eosinophiles	10%
Basophiles	½%
Large mononuclears	9%
Small mononuclears	30%
Transitionals	½%

The above count was made during the interval between attacks, a considerable time having elapsed since the last attack.

November 15, 1910.—Intravenous injection of 0.3 gram Ehrlich's "606." The patient remained in hospital until December 8, 1910. During most of this time she was kept in bed and not exposed to a sufficient degree of cold to induce an attack of hemoglobinuria. Nevertheless, on December 3, without premonitory symptoms, she voided a dark brown urine, which gave a positive guiac test for blood. Wassermann reaction positive.

Case II.—F. L., male, colored, aged seven years.

Admitted to hospital November 6, 1910.

Diagnosis.—Paroxysmal Hemoglobinuria, Congenital Syphilis.

Complaint.—Blood in urine.

Family History.—Father alive and well, mother alive and well. One brother died at two months of age, cause unknown. Mother has had four miscarriages. No positive history of syphilis in either parent.

Past History.—At the age of one month the patient had a conjunctivitis lasting a week. At two and a half months of age, pleurisy, otorrhœa at 18 months of age, pneumonia at one year. Since then has had measles and whooping cough.

Patient was shocked by lightning 18 months ago; since then he has had at times some pain in right leg and occasional swelling of right knee and ankle joints.

Present Illness.—Began in April, 1908, three days before the onset of an attack of measles. After exposure to severe cold patient had a chill, folowed by fever and the passage of "bloody urine." Since that time the patient has had very numerous attacks, as many as three or four in a week. The attacks occur only in cold weather, never in the summer.

Physical Examination.—Normal looking child. Pupils equal and react normally. Teeth appear normal, tonsils enlarged and injected. Lungs and heart normal. Liver and spleen not enlarged. Patellar reflex normal.

Blood Examination.—Fresh specimen showed no poikitocytosis or anisocytosis, no parasites seen.

R. B. C.	5,488,000
W. B. C.	10,280
Hb.	74%

Urine Examination.—Specimen is clear yellow. Sp. Gr. 1020. Reaction acid, no sugar, no albumen, no sediment. Microscopically no abnormal constituents seen. Guiac test for blood negative.

Wassermann reaction positive.

Case III.—J. S., male, white, aged 32, Austrian.

Complaint.—Passage of bloody urine following exposure to cold.

Family History.—Father died at age of 65 of "liver trouble." Mother alive, aged 65 years, has chronic rheumatism. One brother alive and well, one brother dead as result of accident, one half-brother and two half-sisters alive and well.

Past History.—General health has been good. As a child had scarlet fever, measles and chicken-pox. Has had grippe repeatedly and "catches cold" easily. While in the army ten years ago had an attack of arthritis, which kept patient in bed for two weeks, convalescence occupied several weeks. Pain and swelling started first in knee joint, then the hip, shoulder, wrist and temporo-maxillary joints were successively involved. Venereal infection denied.

Present Illness.—Began December 7, 1902. Following exposure to severe cold patient had a chill lasting one-half to one hour, succeeding which there was high fever for two or three hours. The first urine voided following the chill was "bloody." The attack was over in five or six hours. Within a week he had a second and ever since has been subject to attacks whenever he gets very much chilled. They are most frequent during spring and fall, especially during cold damp weather. He never suffers from them during the summer.

Wassermann reaction positive.

The hematological studies carried out on the foregoing cases were directed along the following lines:

1. The demonstration of the peculiar hemolysin characteristic of paroxysmal hemoglobinuria.

2. The determination of the group (according to the iso-agglutination reaction) to which the patients belong and presence or absence of normal iso-hemolysins.

3. Determination of the relation of temperature to the union of (a) amboceptor and corpuscle, (b) complement and amboceptor-corpuscle.

4. Separation of the auto- and iso-hemolysin contained in the same serum, in order to determine if the auto-hemolysin is capable of dissolving those individuals' corpuscles for which the serum in question contains an iso-hemolysin.

5. Resistance of the red blood cells.

6. Wassermann reaction.

7. Effect of the administration of Ehrlich's "606," (a) on the Wassermann reaction, and (b) on the clinical course of the disease.

For all of these studies blood was obtained from an arm vein by means of an aspirating syringe. The syringe was always washed out with sterile sodium citrate solution before using in order to remove the small amount of water which remains in the syringe after boiling and which might cause slight laking of the blood.

Having drawn the blood into the syringe, 2 or 3 cc. are introduced into a centrifuge tube containging 12 cc. of a 1.5% sodium citrate in 0.85% sodium chloride solution for corpuscles. The remainder of the blood is placed in a sterile centrifuge tube and allowed to coagulate at 37° C. in order to obtain serum. After the clot has formed the separation of the serum is facilitated by a few minutes' centrifugalization. The clear serum, which must be perfectly free from hemoglobin, is now pipetted off and transferred to another tube. The further preparation of the corpuscles consists in washing them three times in 0.85% sodium chloride solution to free them from serum and in preparing a 5% suspension of the washed corpuscles in 0.85% sodium chloride solution.

1. *The demonstration of the peculiar hemolysin characteristic of paroxysmal hemoglobinuria.*

The test employed for this demonstration was carried out as follows * and always gave the same result:

Pt. serum 0.25 cc. + Pt. corp. 0.25 cc. (5 % susp.) 0° C. ½ hr. 37° C. 2hrs. = + hemolysis.

Control: Pt. serum 0.25 cc. + Pt. corps. 0.25 cc. (5% susp.) 37° C. 2 hrs. = 0 hemolysis.

At no time did the blood of any of the three cases reported fail to give hemolysis when subjected to the cold-warm test as indicated above, notwithstanding the fact that repeated tests were made, especially in Case I, which has been under observation for over a year. This is in rather striking contrast with the infrequency of positive results reported by Meyer and Emmerich (only 13 times positive in 40 tests) but may possibly be explained by the fact that I made no especial effort to examine serum from my cases at short intervals after attacks.

2. *The determination of the group (according to the iso-agglutination reaction) to which the patients belong, and presence or absence of normal iso-hemolysins.*

It has been shown[6, 7] that all individuals, regardless of health or disease, can be divided into four groups, according to the ability of their serum to agglutinate the corpuscles of other individuals and of their corpuscles to be agglutinated by the serum of other individuals.

This classification may be stated as follows:

Group I. Serum agglutinates no corpuscles. Corpuscles agglutinated by the serum of Groups II, III and IV.

Group II. Serum agglutinates corpuscles of Groups I and III. Corpuscles agglutinated by the serum of Groups III and IV.

Group III. Serum agglutinates corpuscles of Groups I and II Corpuscles agglutinated by serum of Groups II and IV.

Group IV. Serum agglutinates corpuscles of Groups I, II and III. Corpuscles agglutinated by no serum.

The group to which an individual belongs is established shortly after birth and thereafter undergoes no change.[8] A strict classification of individuals according to the iso-hemolytic properties of the blood has not been accomplished since this reaction, unlike the iso-agglutination reaction, is not entirely constant; certain general laws, however, have been formulated as a result of observations on the iso-hemolytic reaction. Thus the serum of Group I, which contains no iso-agglutinin, never contains an iso-hemolysin, while the corpuscles of Group I may or may not in a given case be hemolysed by the serum of a member of Group II, III or IV.

The serum of a given member of Group II may or may not contain an iso-hemolysin, but if it does it can act only against corpuscles of members of Groups I and III, but not necessarily against the corpuscles of all members of these two

* Where the expression "0° C." is used in this paper in describing my own experiments it is to be understood that the tubes were placed in a vessel of ice water ranging in temperature from 0° C. to about 2° C.

groups. Similarly, if a member of Group III contains an iso-hemolysin it can act only against the corpuscles of Groups I and II. The iso-hemolysin of Group IV is effective only against corpuscles of Groups I, II and III. The corpuscles of Group IV are not subject to the action of iso-hemolysin and from what has just been said, the corpuscles of members of the other three groups are never hemolysed by the serum of a member of the corresponding group.

The group to which an individual belongs can be readily determined by testing the agglutinating action of his serum against the corpuscles of the four different groups, or by testing the action of serum from the four different groups against the corpuscles of the individual to be classified. This will be made clearer by taking an example.

To determine the group to which an individual, X, belongs:

	First Method.	37°C. 2 hrs.	I.	II.	III.	IV.
1	Serum X 0.25 cc. + Corp. Gr. I 0.25 cc.		0	+	+	+
2	Serum X 0.25 cc. + Corp. Gr. II 0.25 cc.		0	0	+	+
3	Serum X 0.25 cc. + Corp. Gr. III 0.25 cc.		0	+	0	+
4	Serum X 0.25 cc. + Corp. Gr. IV 0.25 cc.		0	0	0	0

Column I shows the resulting agglutination if X is a member of Group I and similarly, Columns II, III, and IV show the resulting agglutination if X is a member of Group II, III or IV, respectively.

	Second Method.	37°C. 2 hrs.	I.	II.	III.	IV.
1	Corp. X 0.25 cc. + Serum Gr. I 0.25 cc.		0	0	0	0
2	Corp. X 0.25 cc. + Serum Gr. II 0.25 cc.		+	0	+	0
3	Corp. X 0.25 cc. + Serum Gr. III 0.25 cc.		+	+	0	0
4	Corp. X 0.25 cc. + Serum Gr. IV 0.25 cc.		+	+	+	0

Columns I, II, III and IV show the resulting agglutination if X is a member of Group I, II, III or IV, respectively.

An analysis of the above tables shows that in order to classify an individual it is not necessary to test his blood against blood from all four groups. It is sufficient if his serum is tested against the corpuscles of Groups II and III, or if his corpuscles are tested against the serum of Groups II and III.

Thus if the serum of the individual to be classified agglutinates corpuscles of neither Group II nor III, it must belong to Group I. If it agglutinates corpuscles of Group III, and not those of Group II, it must belong to Group II. If it agglutinates corpuscles of Group II and not those of Group III, it must belong to Group III, while if it agglutinates corpuscles of both Groups II and III, it must belong to Group IV.

It is just as easy to determine the group if one tests the corpuscles of the individual in question against the serum of Groups II and III.

By the methods just described it was determined to which groups the cases here reported belonged and the presence or absence of normal iso-hemolysin repeatedly observed. It will be sufficient to give in detail the results of a single such determination.

Serum and corpuscles were obtained, as previously described, from four normal individuals representing Groups I, II, III and IV, also from Case I, G. C., whose group was to be determined. Tests were carried out acording to the following protocol:

PROTOCOL I.—Case I, G. C.

Tube No.	Serum 0.25 cc.	Corps. (5% susp.) 0.25 cc.		Aggl.	Hem.		Aggl.	Hem.
1	Gr. I.	Gr. I.	37°C. 2 hrs.	0	0	37°C. 2 hrs.	0	0
2	"	Gr. II.		0	0		0	0
3	"	Gr. III.		0	0		0	0
4	"	Gr. IV.		0	0		0	0
5	"	G. C.		0	0		0	0
6	Gr. II.	Gr. I.		+	0		+	0
7	"	Gr. II.		0	0		0	0
8	"	Gr. III.		+	0		+	0
9	"	Gr. IV.		0	0		0	0
10	"	G. C.		0	0		0	0
11	Gr. III.	Gr. I.		+	0		+	0
12	"	Gr. II.		+	0		+	0
13	"	Gr. III.		0	0		0	0
14	"	Gr. IV.		0	0		0	0
15	"	G. C.		0	0		0	0
16	Gr. IV.	Gr. I.		+	+	0°C. ½ hr.	+	+
17	"	Gr. II.		+	+		+	+
18	"	Gr. III.		+	0		+	0
19	"	Gr. IV.		0	0		0	0
20	"	G. C.		0	0		0	0
21	G. C.	Gr. I.		+	+		+	+
22	"	Gr. II.		+	+		+	+
23	"	Gr. III.		+	+		+	+
24	"	Gr. IV.		0	0		0	+
25	"	G. C.		0	0		0	+

This experiment shows that the corpuscles of the patient, G. C., are neither agglutinated nor hemolysed by the serum of Groups I, II, III or IV, therefore the patient is a member of Group IV. This is confirmed by the fact that her serum agglutinates the corpuscles of Groups I, II and III. It is further evident that the patient's serum contains normal iso-hemolysin, since it is able to hemolyse the corpuscles of Groups I, II and III at 37° C. without the mixtures having been previously exposed to the cold.

In addition to the normal iso-agglutinin and iso-hemolysin contained in the patient's serum, which is effective against corpuscles of Groups I, II and III without the action of cold (Tubes 21, 22 and 23) there is another hemolysin present peculiar to paroxysmal hemoglobinuria, which only becomes evident after the mixture of serum and corpuscles is subjected to a low temperature followed by a high temperature (Tubes 24 and 25).

Attention is here directed to another point of difference between the action of the hemolysin peculiar to paroxysmal hemoglobinuria and normal iso-hemolysin. I have pointed out elsewhere that normal iso-hemolysis is always accompanied or preceded by iso-agglutination. The above experiment shows that the hemolysis caused by the hemolysin peculiar to paroxysmal hemoglobinuria may occur entirely independently of agglutination (Tubes 24 and 25).

The hemolysin which characterizes the disease with which we are dealing is often referred to as an auto-hemolysin, since the patient's serum is able to bring about the solution of his own corpuscles, but as previous investigators have shown and I have repeatedly confirmed, the patient's serum is able to hemolyse not only his own corpuscles but those of other hemoglobinuric patients and normal individuals, therefore it has an iso-hemolytic, as well as an auto-hemolytic action.

This iso-hemolytic action of the hemolysin peculiar to paroxysmal hemoglobinuria, which becomes evident only by

the cold-warm experiment, is not to be confused with the normal iso-hemolytic activity which may be possessed by the serum of hemoglobinuric patients, as well as normal individuals and which does not require previous chilling for its demonstration.

Bearing in mind the fact that it does not fully define the hemolytic power of the serum, I shall use the term auto-hemolysin to distinguish that property which characterizes the serum of hemoglobinuric patients from the normal iso-hemolytic property which may be possessed by the serum of both normal and hemoglobinuric individuals.

Similar tests carried out on the other two cases showed that Case II, F. L., is also a member of Group IV, while Case III, J. S., is a member of Group III and that the serum of both cases contained, in addition to their auto-hemolysin, normal iso-hemolysin.

It now became of interest to determine if the auto-hemolysin of hemoglobinuric patients could bring about the solution of the corpuscles of all individuals; for example, corpuscles for which the serum in question contained a normal iso-hemolysin.

Before this question can be discussed, certain facts must be given which resulted from the experiments undertaken to solve the next point in the investigation, namely:

3. *Determination of the relation of temperature to the union of (a) amboceptor and corpuscle, (b) complement and amboceptor-corpuscle.*

Divergent views are held on this subject. As previously mentioned, Donath and Landsteiner hold that the union of auto-amboceptor to the corpuscle takes place only at a low temperature, that the union of complement occurs subsequently, and only at a higher temperature. Meyer and Emmerich concur in this view, while Hoover and Stone maintain that a low temperature is necessary, not only for the union of the amboceptor and corpuscle but also for the union of the complement, a higher temperature being necessary, however, for the lytic action of the complement.

It seemed easy to approach this problem by means of ordinary reactivation experiments; accordingly, some of the hemoglobinuric serum was inactivated by heating to 56° C. for 20 minutes and the following test performed: 0.5 cc. Pt. serum ina. + 0.25 cc. Pt. corps. (5% susp.) 0° C. ½ hr. 37° C. 5 min. + 0.25 cc. complement (non-lytic serum of normal individual) 37° C. 2 hrs. Result: no hemolysis. The mixture was then held at 0° C. for ½ hour, followed by 37° C. 2 hours. Result: hemolysis.

The above experiment would seem to indicate that a low temperature was necessary for the union of complement as well as amboceptor; on the other hand, it might be argued that the amboceptor united with the corpuscle during the first exposure to a low temperature, but that dissociation took place when the temperature was elevated before the complement was added, hence the failure of hemolysis at the end of the first exposure of 2 hours at 37° C. The positive result (hemolysis) occurring after the exposure to 0° C., followed by a second exposure of 2 hours at 37° C., might be explained on the assumption that reunion took place between the corpuscle and amboceptor at the low temperature and that complement now being present united as soon as the temperature reached a suitable degree and before dissociation could take place between the amboceptor and corpuscle.

That this explanation is correct seems improbable. Dissociation is said to be hastened by temperatures approaching that of the body and by mechanical measures, such as shaking. In the above experiment mechanical factors were carefully avoided and the exposure to 37° C. was very brief, only five minutes being allowed for the temperature of the mixture to rise from 0°C. to 37° C.

In the next experiment the possibility of dissociation under the influence of temperature was avoided, but mechanical factors (washing the corpuscles) were introduced.

0.5 cc. Pt. serum ina. + 0.25 cc. Pt. corps (5% susp.) 0° C. ½ hour. The corpuscles were then removed by centrifugalization at a low temperature (0° C. to 5° C.) and washed twice with salt solution at 0° C., resuspended in 0.5 cc. salt solution and 0.25 cc. of complement at 0° C. (non-lytic serum of a normal individual) added, while the suspension of corpuscles was still at 0° C. This mixture was then held at 37° C. for 2 hours, and as no hemolysis resulted the temperature was lowered to 0° C. for ½ hour and then again held at 37° C. for 2 hours. Result: no hemolysis.

The failure of hemolysis in this experiment might possibly be ascribed to dissociation of the amboceptor and corpuscle under the influence of the mechanical disturbance of washing.

The following experiment indicates that the explantions thus far offered are not correct. 1 cc. Pt. serum + 0.1 cc. Pt. corps., containing as little salt solution as possible, were subjected to a temperature of 0° C. for ½ hour, then centrifugalized at a low temperature (0° — 5° C.), the supernatent fluid removed and saved for further tests, and the corpuscles washed three times with salt solution at 0° C. to remove all the serum from them. They were then suspended in 0.75 cc. salt solution and kept at 37° C. for 2 hours. Result: no hemolysis. Complement was now added (0.25 cc. of normal non-lytic serum) and the temperature maintained at 37° C. Result: prompt hemolysis.

The following seems to be the only explanation which will harmonize the results of all the foregoing experiments: *Union between the auto-amboceptor and the corpuscle takes place only at a low temperature in the presence of complement; the complement does not enter into the combination, or at least not permanently, at this temperature. Complement does unite with the corpuscle-amboceptor combination at 37° C. with resulting solution of the cell.*

The last experiment further shows that the union between amboceptor and corpuscle is a fairly stable one, since repeated washing at a low temperature and subsequent standing for 2 hours at 37 C. does not cause dissociation.

If the above explanation is correct, then the serum in the last experiment, which was removed after standing in contact with the corpuscles at a low temperature, should have been deprived of its auto-amboceptor, but not of its complement

(provided the proper quantitative relations were observed). The following tests were made to determine these points:

0.25 cc. serum from previous test + Pt. corps. 0.25 cc. (5% susp.) 0° C. ½ hr. 37° C. 2 hrs. = no hemolysis.

0.25 cc. serum from previous test + 0.25 cc. complement (normal non-lytic serum) + Pt. corps. 0.25 cc. (5% susp.) 0° C. ½ hr. 37° C. 2 hrs. = 0 hemolysis.

0.25 cc. serum from above + 0.25 cc. Pt. serum ina. + 0.25 cc. Pt. corps. 0°C. ½ hr. 37° C. 2 hours = + hemolysis.

These three tests show that all of the auto-amboceptor had been removed from the patient's serum by contact with patient's corpuscles at a low temperature, but that complement remained, thus corroborating the findings when the corpuscles were examined and found to have anchored amboceptor, but not complement, at the low temperature.

If this interpretation of the results is correct, it furnishes an example of a hitherto undescribed function of complement; namely, the ability to effect a combination between two other bodies (amboceptor and corpuscle) without itself entering permanently into the combination.

We are now in a position to consider the question previously mentioned as to the ability of the auto-hemolysin contained in the serum of a hemoglobinuric patient to bring about the solution of corpuscles for which the same serum contains an iso-hemolysin.

4. *Separation of the auto- and iso-hemolysin contained in the same serum in order to determine if the auto-hemolysin is capable of dissolving those individuals' corpuscles for which the serum in question contains an iso-hemolysin.*

Reference to Protocol I, of experiments carried out on the serum of Case I, G. C., shows that the serum of this patient contained an iso-hemolysin for the corpuscles of a normal individual belonging to Group I, for one belonging to Group II and for one belonging to Group III (Tubes 21, 22 and 23) in addition to the auto-hemolysin for an individual belonging to Group IV and for her own corpuscles.

In order to determine if the auto-hemolysin is capable of dissolving the corpuscles of the individuals belonging to Groups I, II and III it is first necessary to remove the iso-hemolysin. To this end, serum and corpuscles were obtained as follows:

No. 3 normal individual belonging to Group III.

No. 4 normal individual belonging to Group IV.

No. 5, Case I, G. C., hemoglobinuria patient, Group IV.

A portion of serum 5 (Case I, G. C.) was inactivated by heating at 56° C. for 20 minutes and the experiments were performed as shown in Protocol II.

Tubes 1 to 9 inclusive, in Protocol II are controls and show as follows:

Tube 1 shows that serum 4, which was used as complement contained no iso-hemolysin for corpuscles 3.

Tube 2 shows that serum 5 contained an iso-hemolysin for corpuscles 3 (reading at end of first two hours at 37° C.).

Tubes 3 and 4 show that serum 5 contains no iso-hemolysin for corpuscles 4 and 5 (reading at end of first two hours at 37° C.), but that it does contain an auto-hemolysin for these corpuscles (reading after ½ hour at 0° C. + 2 hours at 37° C.).

Tube 5 shows that the iso-hemolysin in serum 5 was inactivated for corpuscles 3 by heating to 56° C. for 20 minutes.

Tube 6 shows that the auto-hemolysin (if effective against corpuscles 3) had been inactivated by heating to 56° C. for 20 minutes.

Tube 7 shows that the auto-hemolysin contained in serum 5 for corpuscles 5 had been inactivated by heating to 56° C. for 20 minutes.

Tube 8 shows that serum 4 was capable of activating the iso-amboceptor contained in serum 5 for corpuscles 3.

Tube 9 shows that serum 4 was capable of activating the auto-amboceptor contained in serum 5 for corpuscles 5.

PROTOCOL II.

To absorb the iso-hemolysin from hemoglobinuric serum leaving the auto-hemolysin and determine if the latter is capable of dissolving an individual's corpuscles (No. 3) for which the hemoglobinuric serum contains an iso-hemolysin.

1.	Ser. 4, ¼ cc. + Corps. 3, ¼ cc.		37°C. 2 hrs. = 0 hem.
2.	Ser. 5, ¼ cc. + Corps. 3, ¼ cc.	37°C. 2 hrs. = + hem.	0°C. ½ hr. 37°C. 2 hrs. = + hem.
3.	Ser. 5, ⅛ cc. + Corps. 4, ¼ cc.	37°C. 2 hrs. = 0 hem.	0°C. ½ hr. 37°C. 2 hrs. = + hem.
4.	Ser. 5, ¼ cc. + Corps. 5, ¼ cc.	37°C. 2 hrs. = 0 hem.	0°C. ½ hr. 37°C. 2 hrs. = + hem.
5.	Ser. 5 ina., ¼ cc. + Corps. 3, ¼ cc.		37°C. 2 hrs. = 0 hem.
6.	Ser. 5 ina., ¼ cc. + Corps. 3, ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
7.	Ser. 5 ina., ¼ cc. + Corps. 5, ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
8.	Ser. 5 ina., ¼ cc. + Corps. 3, ¼ cc. + Comp. (Ser. 4) ¼ cc.		37°C. 2 hrs. = + hem.
9.	Ser. 5 ina., ¼ cc. + Corps. 5, ¼ cc. + Comp. (Ser. 4) ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = + hem.
10.	Ser. 5 ina., 1½ cc. + Corps. 3, $\frac{8}{100}$ cc. 37°C. 2 hrs. Centrifugalize, save serum, wash corps.		
11.	Ser. tube 10, ¼ cc. + Corps. 3, ¼ cc. + Comp. (Ser. 4) ¼ cc.		37°C. 2 hrs. = 0 hem.
12.	Ser. tube 10, ¼ cc. + Corps. 5, ¼ cc. + Comp. (Ser. 4) ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = + hem.
13.	Ser. tube 10, ¼ cc. + Corps. 3, ¼ cc. + Comp. (Ser. 4) ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = + hem.
14.	Washed corps. tube 10 + NaCl ¾ cc. + Comp. (Ser. 4) ¼ cc.		37°C. 2 hrs. = + hem.
15.	Ser. 5 ina., 1½ cc. + Corps. 3, $\frac{8}{100}$ cc. 0°C. 2 hrs. Centrifugalize, save serum, wash corps.		
16.	Ser. tube 15, ¼ cc. + Corps. 3, ¼ cc. + Comp. (Ser. 4) ¼ cc.		37°C. 2 hrs. = 0 hem.
17.	Ser. tube 15, ¼ cc. + Corps. 5, ¼ cc. + Comp. (Ser. 4) ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = + hem.
18.	Ser. tube 15, ¼ cc. + Corps. 3, ¼ cc. + Comp. (Ser. 4) ¼ cc.		0°C. ½ hr. 37°C. 2 hrs. = + hem.
19.	Washed corps. tube 15 + NaCl ¾ cc. + Comp. (Ser. 4) ¼ cc.		37°.C 2 hrs. = + hem.

Wherever inactive serum was used in the above experiment it is indicated by the abbreviation "ina." Elsewhere active serum was used.

The corpuscles were used in 5% suspension except in tubes 10 and 15, where all the supernatant salt solution after centrifugalization was removed from the corpuscles before they were used.

Tube 10 was to absorb the iso-amboceptor from serum 5 inactive at 37° C. by means of corpuscles 3.

Tube 11 shows that all of the iso-amboceptor for corpuscles 3 had been absorbed from serum 5 inactive in tube 10.

Tube 12 shows that the auto-amboceptor had not been removed from serum 5 inactive in tube 10.

Tube 13 shows that the auto-amboceptor contained in serum 5 inactive was capable of dissolving an individual's corpuscles (corpuscles 3) for which the hemoglobinuric serum contained an iso-hemolysin, Q. E. D.

Tube 14 shows that the corpuscles in tube 10 had anchored an iso-amboceptor from serum 5 inactive, which was not separated from the cells by washing twice at room temperature with 10 cc. salt solution at each washing.

Tube 15 was to absorb the iso-amboceptor from serum 5 inactive at 0° C. by means of corpuscles 3. (I have previously

shown that the auto-amboceptor cannot be absorbed even at 0° C. except in the presence of complement. The remaining tubes confirmed this statement).

Tubes 16, 17, 18, 19 gave results identical with those given by tubes 11, 12, 13, 14, again proving that the auto-hemolysin of hemoglobinuric serum is capable of dissolving an individual's corpuscles for which the serum contains an iso-hemolysin.

Having absorbed the iso-hemolysin from hemoglobinuric serum and left the autohemolysin, it seemed desirable, in order to complete this part of the study, to absorb the auto-hemolysin from hemoglobinuric serum and leave the iso-hemolysin. This was readily accomplished in the following manner:

Blood was obtained from—

No. 1. A normal individual belonging to Group I.

PROTOCOL III.

To absorb the auto-amboceptor from hemoglobinuric serum leaving the iso-amboceptor.

1. Ser. 5, ¼ cc. + Corps. 1, ¼ cc. 37°C. 2 hrs. = + hem. 0°C. ½ hr. 37°C. 2 hrs. = + hem.
2. Ser. 5, ¼ cc. + Corps. 4, ¼ cc. 37°C. 2 hrs. = 0 hem. 0°C. ½ hr. 37°C. 2 hrs. = + hem.
3. Ser. 5, ¼ cc. + Corps. 5, ¼ cc. 37°C. 2 hrs. = 0 hem. 0°C. ½ hr. 37°C. 2 hrs. = + hem.
4. Ser. 4. ¼ cc. + Corps. 5. ¼ cc. 37°C. 2 hrs. = 0 hem. 0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
5. Ser. 5 ina., ¼ cc. + Corps. 1, ¼ cc. 37°C. 2 hrs. = 0 hem. 0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
6. Ser. 5 ina., ¼ cc. + Corps. 5, ¼ cc. 0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
7. Ser. 5 ina., ¼ cc. + Corps. 1, ¼ cc. + Comp. (ser. 4) 1/10 cc. 37°C. 2 hrs. = + hem.
8. Ser. 5 ina., ¼ cc. + Corps. 5, ¼ cc. + Comp. (ser. 4) 1/10 cc. 0°C. ½ hr. 37°C. 2 hrs. = + hem.
9. Ser. 5, 1 cc. + Corps. 5, 1/20 cc. 0°C. ½ hr. Centrifugalize at 0°C. same serum and wash corpuscles three times at 0°C.
10. One-half the washed corps. from tube 9 + NaCl 0.45 cc. 37°C. 2 hrs. = 0 hem.
11. One-half the washed corps. from tube 9 + NaCl 0.45 cc. + Comp. (ser. 4) 1/10 cc. 37°C. 2 hrs. = + hem.
12. Ser. tube 9, ¼ cc. + Corps. 5, ¼ cc. 0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
13. Ser. tube 9, ¼ cc. + Corps. 5, ¼ cc. + Comp. (ser. 4) 1/10 cc. 0°C. ½ hr. 37°C. 2 hrs. = 0 hem.
14. Ser. tube 9, ¼ cc. + Corps. 5, ¼ cc. + Ser. 5 ina., ¼ cc. 0°C. ½ hr. 37°C. 2 hrs. = + hem.
15. Ser. tube 9, ¼ cc. + Corps. 1, ¼ cc. 37°C. 2 hrs. = + hem.

Wherever inactive serum was used in the above experiments it is indicated by the abbreviation "ina." Elsewhere active serum was used.

The corpuscles were used in 5% suspension except in tube 9, where all the supernatant salt solution after centrifugalization was removed from the corpuscles before they were used.

No. 4. A normal individual belonging to Group IV.

No. 5. Case I, G. C., hemoglobinuric patient, Group IV.

Tubes 1 to 8 inclusive are controls and show as follows:

Tube 1 shows that serum 5 contains an iso-hemolysin for corpuscles 1 (reading at the end of first 2 hours at 37° C.).

Tubes 2 and 3 show that serum 5 contains an auto-hemolysin for corpuscles 4 and 5 (reading after ½ hour at 0° C. and 2 hours at 37° C.).

Tube 4 shows that serum 4 contains neither iso- nor auto-hemolysin for corpuscles 5, therefore it can be used for complement, provided it is able to reactivate serum 5 inactive.

Tube 5 shows that both the iso- and auto-hemolysin contained in serum 5 for corpuscles 1 were inactivated by heating to 56° C. for 20 minutes.

Tube 6 shows that the auto-hemolysin contained in serum 5 for corpuscles 4 was inactivated by heating to 56° C. for 20 minutes.

Tubes 7 and 8 show that serum 4 (complement) is capable of reactivating both the iso- and auto-amboceptor contained in serum 5 inactive.

Tube 9 was to absorb the auto-amboceptor from serum 5 by means of corpuscles 5 at 0° C. Hemolysis was prevented by keeping the mixture at a low temperature until after the serum had been removed from the corpuscles and the latter thoroughly washed with salt solution.

Tube 10 shows that the corpuscles did not anchor, at least not permanently, both auto-amboceptor and complement at 0° C.

Tube 11 shows that the corpuscles did anchor the auto-amboceptor at 0° C., that dissociation did not occur as a result of thorough washing of the corpuscles and that complement united at 37° C. with consequent solution of the corpuscles. This and tubes 12, 13, 14 are a repetition and confirmation of experiments done many times under subhead 3; namely: Determination of the relation of temperature to the union of (a) amboceptor and corpuscle (b) complement and amboceptor-corpuscle.

Tube 12 shows that serum 5 after absorbtion with corpuscles 5 in tube 9 at 0° C. was unable to dissolve corpuscles 5.

Tube 13 shows that the failure of hemolysin in tube 12 was not due to lack of complement.

Tube 14 shows that the failure of hemolysis in tube 12 was due to lack of auto-amboceptor only.

Tube 15 shows that the auto-amboceptor was absorbed from serum 5 in tube 9, leaving iso-amboceptor and complement, Q. E. D.

Hoover and Stone were able to absorb the auto-amboceptor from hemoglobinuric serum in the absence of complement, as indicated by the following quotation, to which reference has previously been made: "Thus we have shown that if in two stages, 10 drops of a 10% suspension of red cells be added to (1 cc.) the serum and exposed to cold for one hour each time, the amboceptor can be exhausted from the inactivated hemoglobinuric serum." It seems probable that this result is to be explained on the basis of a mechanical removal due to the relatively large amount of corpuscles used. Even so they found it necessary to absorb in two stages.

In my efforts to separate the auto- and iso-amboceptor in hemoglobinuric serum I found it necessary to use the minimum quantity of corpuscles which would completely remove the one in order that the other be left. In case an excess of corpuscles was employed both auto- and iso-amboceptor would be removed.

5. *Resistance of the red blood corpuscles.*

Certain investigators have observed that the red blood cells of hemoglobinuric patients studied by them were less resistant to hypotonic salt solution than normal, while other investigators have found no difference between normal corpuscles and the corpuscles of their patients in relation to hypotonic salt solution. Dr. Helen Watson kindly tested this point for me in my three cases. The corpuscles of Cases I and II were tested on two occasions, an interval of about two months elapsing between tests. The corpuscles of Case III were only

tested once. The corpuscles of all three patients showed definitely increased resistance to hypotonic salt solution. The only exception to this rule was Case II, whose corpuscles, at the time of the second test, showed the same resistance as those of several normal individuals, tested at the same time, but on the occasion of the first test they showed a markedly greater resistance than normal corpuscles.

It has been shown by numerous investigators that the destruction of erythrocytes during the paroxysms of this disease is not due to any inherent weakness of the cells but to a peculiar action of the serum of these patients and that this serum is capable of dissolving not only the corpuscles of hemoglobinuric patients, but also those of normal individuals. With the exception of the variation of resistance of hemoglobinuric corpuscles I know of no reason why they may not be regarded as normal corpuscles. That they show a variable and sometimes greater than normal resistance may possibly be explained in the following way.

It seems reasonably certain that the individual corpuscles of any person differ in their resistance. This idea is based on the fact that if one sets up a series of tubes containing falling strengths of salt solution (3 cc. in each tube) and introduces one drop (approximately 1/30 cc.) of corpuscles into each tube, it will be observed that hemolysis begins in a dilution of about 0.475% NaCl but is not complete until a dilution of about 0.30% is reached. That is, in the tube containing 0.475% NaCl only a few of the introduced corpuscles are dissolved. That these few are dissolved and the others are not seems to be best explained on the assumption that those corpuscles which were dissolved were less resistant to the action of hypotonic salt solution than the remainder of the corpuscles. That the small amount of serum (or iso-tonic salt solution) introduced with the drop of corpuscles plays but little part in altering the tonicity of the mixture is evident from the proportion used, 3 cc. 0.475% NaCl + 1/30 cc. 0.85% NaCl gives 3 1/30 cc. of a 0.479% solution. The slight increase of tonicity of the 0.475% solution due to the addition of the salt carried over with the one drop of corpuscles and to the solution of a part of the corpuscles, might protect the remainder of the corpuscles, but this explanation cannot serve in the case of a 0.40% salt solution where only a portion of the added corpuscles undergoes solution. In this case 1/30 cc. 0.85% NaCl added to 3 cc. of 0.40% NaCl brings the concentration of the resulting mixture only up to 0.405%, which is still relatively far below that in which hemolysis first appeared (0.475%). In the above examples the entire drop of corpuscles has been considered as the equivalent of 0.85% salt solution, whereas it probably has something less than this value in raising the tonicity of the mixture.

Assuming that individual corpuscles of a person vary in their resistance to hypotonic salt solution, it seems not unlikely that they differ in their resistance to other destructive agents, and that during an attack of paroxysmal hemoglobinuria those corpuscles possessing the least resistance would be the ones destroyed, leaving the more resistant ones. If this theory is correct, a resistance test taken shortly after an attack of hemoglobinuria would show increased resistance, while a test taken at a considerable interval after an attack would show normal relations. The correctness of this theory remains to be proven.

6. *The Wassermann Reaction.*

In the reported cases of paroxysmal hemoglobinuria, evidence of syphilis, usually congenital, has been observed so often as to give weight to the suggestion frequently made that the latter perhaps stands in an etiological relationship. All efforts to find an infectious agent in the blood of these patients have, so far as I am aware, failed. The idea advanced that the disease is due to an auto-immunization resulting from a resorption by the patient of his own blood has never been proven and there is but scant evidence in its support. Of the various suggestions made that of congenital syphilis seems to have most evidence in its favor.

Dr. C. R. Austrian kindly did the Wassermann reaction of the three cases here reported. All gave positive reactions. Tests were done on both the father and mother of Case I, and the mother was found also to give a positive reaction. The father of Case II gave a negative reaction and although the mother was not tested, the history of four miscarriages in the mother is suggestive.

Case III gave no history of syphilis, but had, as stated, a positive Wassermann reaction.

7. *The effect of the administration of Ehrlich's "606," (a) on the Wassermann reaction; (b) on the clinical course of the disease.*

On November 15, 1911, Case I was given 0.3 gram "606" intravenously. She remained in the hospital until December 8, 1910. During most of this time she was kept in bed and not exposed to a sufficient degree of cold to induce an attack of hemoglobinuria. Nevertheless, on December 3, without premonitory symptoms, she voided a dark brown urine which gave a positive guiac test for blood, as is stated in the case history. The Wassermann reaction was still positive.

After the child's discharge from the hospital, she had no further attack until about March, 1911. The freedom from attacks during the interval, the patient, since the onset of the disease, never having gone so long during cold weather without attacks, led the mother to believe that a cure had been effected. Accordingly, of her own initiative and without my knowledge, she frequently sent the child out to play during cold, damp weather, without hat or coat, in order to see if an attack would be induced. Notwithstanding this marked improvement in the clinical condition, the patient's serum is still able, in vitro, to hemolyse her own and other corpuscles, when subjected to the cold-warm test, although not to the same degree, I think, as before the administration of "606," and she still has a positive Wassermann reaction.

It seems advisable to repeat the administration of "606" in this case, and I hope to have the opportunity of trying it on the other two cases before the onset of cold weather.

Summary.

The serum of patients suffering from paroxysmal hemoglobinuria contains a complex hemolysin, of amboceptor-complement nature, which is capable of bringing about the

solution of the patient's own corpuscles, corpuscles of other paroxysmal hemoglobinuric patients, and of all other individuals, as far as tested.

Patients suffering from paroxysmal hemoglobinuria are not confined to one group, as determined by the iso-agglutination reaction, and their serum may contain normal iso-hemolysin in addition to the hemolysin characteristic of their disease.

The auto-amboceptor may be absorbed from patient's serum, leaving the iso-amboceptor and conversely the iso-amboceptor may be absorbed, leaving the auto-amboceptor, thus enabling each to be tested separately on any given set of corpuscles.

Only the amboceptor component of the hemolysin of paroxysmal hemoglobinuria is peculiar to the disease. The complement differs in no way, so far as tested, from that present in normal serum.

The amboceptor peculiar to paroxysmal hemoglobinuria differs from other known hemolytic amboceptors in that it will unite with the red blood corpuscles only at a low temperature in the presence of complement, and furthermore, in that it is capable of bringing about the solution of the patient's own cells (auto-hemolytic action) and those of other members of the group to which the patient belongs, as well as the cells of members of other groups.

Hemolysis due to the auto-hemolysin of paroxysmal hemoglobinuria unlike normal iso-hemolysis, may occur entirely independently of agglutination.

The red cells of the three cases here reported showed a variable and usually increased resistance to hypotonic salt solution. Never a resistance less than that of normal corpuscles.

All three cases gave a positive Wasserman reaction.

Case I received 0.3 gram Ehrlich's "606" in November, 1910. Prior to that time the patient, never, since the onset of the disease, went more than two or three weeks, except during summer, without an attack of hemoglobinuria, and often had attacks at shorter intervals. Since receiving "606," the Wassermann reaction has remained positive, but the patient has, up to the present time, May, 1911, suffered but two attacks, although repeatedly exposed to cold.

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THE CALCIFICATION OF THE COSTAL CARTILAGES, THE CARDIO-THORACIC INDEX AND OTHER SIGNS OF PULMONARY TUBERCULOSIS.

By W. W. BOARDMAN, M. D.,

Assistant Physician, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital,

AND

H. KENNON DUNHAM, M. D., Cincinnati.

The radiographic diagnosis of pulmonary tuberculosis is based upon more or less characteristic alterations in the shadows of the hilum and lung fields, and by some radiographers also upon alterations in the shadow of the heart, diaphragm and thoracic walls. The alterations in the shadows of the hilum and lung fields are dependent upon morbid changes present in the lungs and hilum, as a result of the local activity of the tubercle bacilli. The alterations in the shadows of the heart, diaphragm and thoracic walls are due to changes in these structures, and are generally considered as either secondary changes, or as predisposing factors to the pulmonary disease. In a previous article[1] we have considered at length the appearance and diagnostic value of the shadows of the hilum and lung fields. At this time we wish to consider the nature and diagnostic value of the alterations in the shadows of the heart, diaphragm and thoracic walls.

On reviewing the literature one finds that there are many alterations in the shadows of these structures, to which more or less importance has been attached. The most frequently mentioned are the "small pendulous heart," and the calcification of the rib cartilages. Other alterations noted are narrow interspaces, contraction of one side of the thoracic wall, decrease in the angle made by the neck muscles and the clavicle, various abnormalities in the shape of the upper aperture of the chest cavity, alterations in the outline and height of the diaphragm, etc.

For the studies here reported, the radiographs taken in

[1] See first paper in this number.

connection with the stereo-rœntgenographic work done in the Research Laboratory of the Phipps Dispensary of the Johns Hopkins Hospital, were used. In taking these plates the relative position of X-ray tube, patient, and photographic plate was the same in every case. As previously reported, each patient radiographed was subjected to careful clinical examination and the conclusions, independently arrived at by these different methods of examination, compared. In this series only those cases are considered in which there was complete agreement in the findings by both clinical and radiographic examination.

Turning now to a consideration of the heart in pulmonary tuberculosis, we wished to determine, if possible, the occurrence of any characteristic alteration in the heart shadow which might be of diagnostic value. As previously stated, the so-called "small pendulous heart" is most frequently mentioned by radiographers as a sign of value. By some it is considered as merely indicating a marked predisposition to pulmonary tuberculosis; by others, however, it is considered a change secondary to tuberculous infection of the lungs. In studying this question a series of ninety-eight cases was examined, in which the clinicians had given special attention to the condition of the heart. As a basis of comparison of individual cases or of groups of cases, it is evident that the actual area of the cardiac shadow would be valueless, as this must vary with the size, age, sex, etc., of the patient. It was, therefore, necessary to consider the size of the heart shadow in comparison with the size of some other shadow, the original of which varies in the same way as does the heart with the size, age, sex, etc., of the patient. To this end the greatest transverse diameter of the heart shadow was compared with the greatest transverse diameter of the chest shadow and the resulting ratio, which therefore expresses the size of the heart in relation to the size of the chest, was termed the Cardio--Thoracic Index.

TABLE I

SHOWING THE INFLUENCE OF SEX UPON THE CARDIO-THORACIC INDEX.

Sex	No. of Cases	Cardio-Thoracic Index		
		Average	Max.	Min.
Male	47	0.446	0.52	0.35
Female	33	0.430	0.50	0.37

Table I shows that in the cases examined the average cardio-thoracic index, independent of age or physical condition, was slightly greater in the males than in the females.

TABLE II

SHOWING THE INFLUENCE OF AGE UPON THE CARDIO-THORACIC INDEX.

Age	No. of Cases	Cardio-Thoracic Index		
		Average	Max.	Min.
0-5 years	3	0.456	0.47	0.39
5-15 years	11	0.446	0.50	0.41
15-30 years	45	0.450	0.50	0.37
30-40 years	15	0.443	0.52	0.39
40-50 years	4	0.42	0.52	0.40
50-60 years	2	0.42	0.45	0.40

Table II shows the cardio-thoracic index, independent of sex or physical condition, to be practically constant in the different age periods, with a slight tendency to decrease in later life.

TABLE III

SHOWING THE INFLUENCE OF PULMONARY TUBERCULOSIS UPON THE CARDIO-THORACIC INDEX.

Stage of Disease	No. of Cases	Cardio-Thoracic Index		
		Average	Max.	Min.
Neg.	14	0.452	0.50	0.35
Doubt.	16	0.440	0.48	0.39
I Stage	6	0.435	0.46	0.41
II Stage A	14	0.437	0.50	0.37
II Stage B	13	0.449	0.48	0.40
III Stage	17	0.438	0.52	0.39

Table III is of special importance. As will be seen, the cases are divided into Non-Tuberculous, Doubtful and Tuberculous. The Tuberculous are sub-divided into four groups depending on the stage of the disease,—first stage, early second stage, late second stage and third stage. Here the cardio-thoracic index is practically constant in the different groups, with, however, a slight tendency for the average to be smaller in the tuberculous than in the non-tuberculous and doubtful cases. However, one fact must be borne in mind, and this is, that the cardio-thoracic index varies between fairly wide limits in the individual cases, both normal and tuberculous, as is shown by the maximum and minimum indices given in the various tables.

TABLE IV

SHOWING THE INFLUENCE OF CARDIO-VASCULAR DISEASE UPON THE CARDIO-THORACIC INDEX.

Disease	No. of Cases	Cardio-Thoracic Index		
		Average	Max.	Min.
Myocarditis	5	0.564	0.59	0.54
Mitral Insufficiency	7	0.502	0.57	0.43
Aneurism	6	0.543	0.58	0.52

Table IV shows a high cardio-thoracic index in 18 cases with definite cardiac lesions. These cases naturally are not included in the previous tables.

From our pathological experience we know that a small heart is a common finding in individuals dead of chronic wasting disease, such as tuberculosis, carcinoma, etc. Here the small heart is merely an expression of the general wasting and is not characteristic of any special disease process. Thus in one of our cases, dead of carcinoma of the oesophagus, the radiograph taken just before the autopsy showed a cardio-thoracic index of 0.37. However, in our third stage cases (Table III) which were all ambulatory, the average cardio-thoracic index was 0.438 with the maximum 0.52 and a minimum of 0.39. Evidently, then, the small heart is far from constant even in third stage cases. Now as the value of the radiographic examination must depend upon one's ability to discover disease processes at a time when the clinician is still doubtful, or anxious for confirmation of his findings, it is use-

less to attempt to base a diagnosis upon changes which are neither constant nor characteristic, even in the late stages of the disease.

From the preceding we may safely conclude that the average cardio-thoracic index is practically constant in the different age periods, that it is slightly smaller in females than in males, and that in the tuberculous, although on the average it shows a very slight tendency to be somewhat smaller than in the non-tuberculous, this average tendency is so slight and varies so widely in individual cases, that it cannot be considered a sign of any value in the radiographic diagnosis of pulmonary tuberculosis.

The pendulous character of the heart shadow, sometimes described as significant of pulmonary infection, is dependent for its appearance upon the small size of the heart and must therefore share with the cardio-thoracic index the same lack of value as a diagnostic sign.

Regarding the occurrence and diagnostic value of calcification of the rib cartilages, two theories have been advanced. The one that calcification, by interfering with the free movement of the thoracic walls, renders proper aeration of the apices impossible and therefore acts as a strong predisposing factor to pulmonary tuberculosis, the other that the calcification is secondary to the pulmonary disease and depends upon altered metabolic processes. Pathological experience seems to favor the latter view. In tables V-VII, the results of the investigation of 153 cases are tabulated. Cases showing complete calcification of the first cartilage, with or without calcification of the other cartilages, are designated positive. Cases showing partial calcification of the first cartilage, with or without partial calcification of the other cartilages, are designated slight.

TABLE V

Showing the Influence of Sex upon the Calcification of the Rib Cartilages.

		Calcification		
Sex	No. of Cases	% +	% Slight	% —
Male	85	30	22	48
Female	68	17	17	66

Table V shows that calcification was more common in the male cases, independent of age and physical condition.

TABLE VI

Showing the Influence of Age upon Calcification of the Rib Cartilages.

		Calcification		
Age	No. of Cases	% +	% Slight	% —
0-5 years	6	0	0	100
5-15 years	20	0	0	100
15-30 years	78	19	17	64
30-40 years	29	33	33	34
40-50 years	9	40	47	13
50-60 years	9	68	32	0
60-70 years	2	50	50	0

Table VI shows that calcification ran parallel with the age.

TABLE VII

Showing the Influence of Pulmonary Tuberculosis upon Calcification of the Rib Cartilages.

		Calcification		
Stage of Disease	No. of Cases	% +	% Slight	% —
Neg.	37	36	28	36
Doubt.	35	10	27	63
I Stage	9	0	10	90
II Stage A	37	19	22	59
II Stage B	16	22	7	71
III Stage	19	46	5	54

Table VII shows that calcification was present in a large percentage of the non-tuberculous cases. It also shows that calcification was absent in the first stage of the disease and increased in frequency with advance in the disease; however, only in the third stage cases did the percentage of positive cases exceed that found in the non-tuberculous cases. It might be mentioned that the patients comprising the third stage group were slightly older than those comprising the non-tuberculous group.

From these tables we may conclude that calcification of the rib cartilages, especially the first, is more common in males than in females, that it increases in frequency with advancing years and finally, that its incidence in pulmonary tuberculosis is only accidental, or a late secondary change, and that its occurrence is of no diagnostic significance whatever in the individual case.

The size of the aortic shadow was studied in relation to the size of the heart but nothing of importance in regard to the diagnosis of pulmonary tuberculosis was determined.

TABLE VIII

Showing the Absence of Any Relation Between the Width of the 2nd Interspace and Pulmonary Tuberculosis.

		Width of 2nd Interspace		
Stage of Disease	No. of Cases	Average	Max.	Min.
Neg.	36	3.0 cm.	4.4 cm.	1.5 cm.
Doubt.	35	2.7 cm.	4. cm.	1.8 cm.
I Stage	9	2.9 cm.	3.8 cm.	2.2 cm.
II Stage A	37	2.9 cm.	4.5 cm.	2. cm.
II Stage B	16	3.3 cm.	4. cm.	2.5 cm.
III Stage	20	2.8 cm.	4. cm.	1.8 cm.

Another sign to which attention is sometimes called is the presence of narrow interspaces in individuals suffering from pulmonary tuberculosis. The width of the 2nd interspace in the left midclavicular line was measured and the results recorded in table VIII. From this it is seen that no apparent relation exists between the width of this interspace and the presence or absence of pulmonary infection. Whether we may take the width of the 2nd interspace as a basis for comparison is, however, open to argument.

TABLE IX

Showing the Absence of Any Relation Between the Angle of the 6th Rib and Pulmonary Tuberculosis.

Stages of Disease	No. of Cases	Angle of 6th Rib		
		Average	Max.	Min.
Neg.	36	100°	104	85
Doubt.	35	97°	103	99
I Stage	9	101°	105	97
II Stage A	37	99°	104	97
II Stage B	16	100°	103	80
III Stage	22	97°	109	85

No very absolute measurements could be made of the angle of the ribs, but in table IX we have recorded the average angle made by the spine and the sixth rib on the left side. Apparently no relation exists between this angle and pulmonary tuberculosis.

The position in which our cases were radiographed made it impossible to study the shape of the upper aperture and alterations in the angles of the neck muscles.

No definite conclusions were reached from our study of the height of the diaphragm, since the average height was about the same in the tuberculous and non-tuberculous cases and the variation in individual cases was very great. There are, however, several interesting features about the diaphragm shadow, especially the occurrence of irregularities, which are worthy of more extended consideration, especially in connection with post mortem examinations.

In conclusion, we believe we are justified in saying that these signs—small pendulous heart, calcified cartilages, narrow interspaces, and excessive sloping of the ribs—are not only valueless, but are absolutely misleading, if considered as positive signs in the radiographic diagnosis of pulmonary tuberculosis.

EXPERIMENTAL STUDIES ON TUBERCULO-PROTEIN HYPERSENSITIVENESS AND THEIR POSSIBLE APPLICATIONS.[1]

By Allen K. Krause, M. D., Saranac Lake, N. Y.

It gives me great pleasure to appear before the Laennec Society as an envoy of the laboratory whose founder, Dr. Edward L. Trudeau, has so often acknowledged his indebtedness to the men of the Johns Hopkins Medical School, who by their generous advice and assistance contributed in no small measure to the success of his work at Saranac Lake.

Ever since Koch's discovery of tuberculin it has been universally taught and believed that the tuberculous animal differs fundamentally from the non-tuberculous animal in its response to injections of derivatives of the tubercle bacillus. The tuberculous animal becomes acutely ill several hours after a subcutaneous injection of tuberculin: it suffers from weakness and prostration and a rise of temperature, and at the same time there are evidences, such as increased cough and expectoration in pulmonary disease, or swelling, pain and redness in joint or glandular involvement, that there is an exacerbation of the disease at the focus. Besides this, at the site of injection there is frequently an area of redness, swelling and pain. The tuberculous animal is therefore found to react to tuberculin in three different ways, to which the terms general, focal, and local or puncture reactions have been applied. It was also discovered by Babes and Proca that if tubercles were induced in an animal by the intravenous injection of dead tubercle bacilli, such animals would likewise react to tuberculin with general, focal, and local signs and symptoms. The general reaction is in both instances considered to be some kind of an intoxication, while the focal and local reactions are forms of inflammation.

Such animals were therefore said to be specifically sensitive to tuberculin; and, as our knowledge of the products of the bacillus extended, it was found that practically every preparation that contained bacillary protein could bring about reactions in animals that harbored tubercles set up by living or dead bacilli. Bacillary emulsion, T. O., T. R., water extract, bacillary filtrate, precipitated tuberculin and a host of other preparations were all like old tuberculin in that extremely small amounts of them rendered the animals ill.

At the same time it was noted that healthy, non-tuberculous animals could sustain relatively enormous doses of tuberculin and tuberculo-derivatives without harm. Although some workers, particularly Landmann, by methods of concentration succeeded in obtaining from tubercle bacilli products that would poison the healthy animal in moderate amounts, still the non-tuberculous always resisted much larger doses of any given preparation than the tuberculous. The healthy animal was accordingly considered to be insensitive to tuberculin and its related products. More than this, the claim was generally made that the animal without specific tubercles could not in any way be made sensitive to tuberculo-protein. Only within the last year no less an authority than Hamburger has come to this conclusion, and within the past two or three months, Kraus, Loewenstein and Volk have supported his contention on experimental evidence, while Wassermann, Pappenheim and von Pirquet have recently voiced the same assumption.

Since every theory that has tried to explain the so-called tuberculin reaction is based on evidence that has denied the possibility of sensitizing non-tuberculous animals with derivatives of the bacillus, Baldwin's announcement, made a year ago, that he had succeeded in doing just this thing was of the greatest importance. It is this work and further ap-

[1] Address delivered before the Laennec Society, Johns Hopkins Hospital, April 24, 1911.

plications of it and the bearing they may have on some of the problems of tuberculosis that I wish to go over with you to-night.

Three years before Baldwin, in 1907, Rosenau and Anderson had intoxicated previously sensitized guinea-pigs with an extract of human tubercle bacilli, so that after a subcutaneous or intraperitoneal injection a few of their animals showed mild symptoms of illness that consisted of restlessness, scratching the nose, irregular respiration, tremor and weakness. They did not follow up this work with further experimentation.

Baldwin sensitized guinea-pigs by the ordinary methods of intraperitoneal or subcutaneous injections of a derivative of the tubercle bacillus. As a rule his preparation was a water-extract-filtrate of the micro-organisms. He obtained this by digesting at 50° C. in distilled water the powder derived from thoroughly washed, dried, pulverized cultures, that had been grown in broth media. After extracting the powder for a day or two, he filtered the supernatant extract-emulsion through a Berkefeld bougie. The filtrate was a material that was freed from bacilli and which very likely contained no other organic constituents except bacillary proteins. Since the organisms were very carefully washed when they were separated from the culture media it is hardly possible that any protein constituents of the broth were carried over with the bacilli except in very negligible quantity. By using this material the contingency of a broth protein sensitization was avoided, and the results of the subsequent experiments could be interpreted as being due to the effect of bacillary protein.

If now a normal animal was treated with a single dose of a small amount of such a water-extract it was found that two or three weeks later it would respond to a second or toxic injection of bacillary protein with all the symptoms of acute anaphylaxis, dying as a rule in from three to six minutes. The material that was used for this second or toxic injection was usually the unfiltered, supernatant extract-emulsion which I have already mentioned. This is the product which Koch described at T. O. It is an extract of the bacilli, and, since it contains the ground-up bodies of the organisms, it is an emulsion as well: we have for this reason usually designated it as extract-emulsion in our work.

Although Baldwin and I found that a small amount of tuberculo-protein would sensitize an animal if it was introduced by almost any parenteral route, it soon appeared that not every way was available for the second injection if toxic symptoms were to be elicited. Baldwin practised toxic injections by way of the peritoneum and subcutaneous tissue without result, and on account of operative shock he got obscure or questionable results with intracerebral and intracardial injections. By using the postorbital method of injection, which had been already described by Gay and Southard, he succeeded in producing acute anaphylaxis almost invariably in sensitized animals. The symptoms were sharp and definite. For a minute or so following the injection the animal was apparently well and normal. It then began to scratch its nose, to cough spasmodically, and to go through "bucking" movements. Dizziness, convulsions and coma rapidly succeeded each other and in a very few minutes the animal was dead. Respiratory distress dominated the picture throughout the attack. At first deep and labored and perceptibly slowed, the thoracic excursions became greater and greater and more and more delayed, until approaching death was signalized by a few tremendous inspirations which toward the end were as much as thirty or forty-five seconds apart. There was no mistaking the character of the symptoms. They were an exact replica of what had been so often described as the anaphylactic shock caused by other proteins. Nor were the pathological findings any less typical. All the animals, that died in this way, had the large, white, blown-out lungs that Auer and Lewis had proved to be characteristic, the pathological anatomy of which has so recently been worked out by Schultz and Jordan. The epicardial hemorrhages to which attention was called by Gay and Southard were also a constant feature.

The amounts that Baldwin usually used were one or two cubic centimeters of water extract intraperitoneally to sensitize a full-grown guinea-pig, and one-half to one cubic centimeter of extract-emulsion postorbitally to intoxicate it fatally. I found later that I could satisfactorily sensitize an animal with 0.01 cc. water extract given intradermically, bring on fatal anaphylaxis with 0.05 cc. extract-emulsion postorbitally, and cause symptoms with 0.03 cc. extract-emulsion postorbitally. The last named quantities are represented by 0.05 mg., 0.9 mg. and 1.6 mg. dry weight respectively.

Such experiments showed us at once that we had succeeded in putting non-tuberculous animals in such a condition that in one respect they resembled tuberculous guinea-pigs: that is, that a fraction of a milligram of tuberculo-protein would make them violently ill. Let us see how the similarity worked out after further experimentation. Let us remember too, that up to this point our information comprised the following facts: the normal, non-tuberculous animal can tolerate the injection of large amounts of our tuberculo-preparations—1.0 cc. extract-emulsion postorbitally, at least 5.0 cc. intravenously, and at least 10 or 15 cc. intraperitoneally without effect; less than a milligram postorbitally will bring about an acute and fatal intoxication in a sensitized non-tuberculous animal; and a fraction of a milligram, introduced subcutaneously or intraperitoneally, will kill a tuberculous guinea-pig with a focal and general reaction that comes on several hours after the injection of the antigen.

I have said that Baldwin failed to poison sensitized guinea-pigs by intraperitoneal injections. As a general thing it is impossible to do so, but in a few very highly sensitive animals I have succeeded in inducing symptoms of illness. I used moderate-sized toxic doses. A citation of a couple of the experiments will show what occurred.

ANIMAL 1.—Sensitized 82 days previously. Injected intraperitoneally with 1.5 cc. E. E. 161.

Result.—The animal seems normal and runs around for about 10 minutes after the injection. Then symptoms of illness begin to develop rapidly. It drags its hind legs, becomes very weak and lies down on its side. These symptoms continue for 10 minutes,

when they begin to subside. Within a half hour after the injection the animal has almost regained its normal condition.

ANIMAL 2.—Sensitized 126 days previously. Injected intraperitoneally with 2.5 cc. E. E. 161.

Result.—No symptoms for 10 minutes. Then the animal becomes weak and staggers around on the floor. The respiration is slow and labored with marked heaving of the chest. The animal slowly recovers from the symptoms.

Here in certain selected animals I get symptoms of illness from an intraperitoneal injection. The fundamental character of the reaction must be the same as that which occurs when I inject postorbitally. But the reaction expresses itself differently. In the latter case, there is a fulminant process that ends in death in a very few minutes; in the former, there is a prolonged chain of symptoms that come on gradually, are much less severe and terminate in recovery. If, now, I make an intravenous, toxic injection on a sensitized animal, I find that it will have the same result as a postorbital one. If, however, I inject subcutaneously, I elicit no symptoms. I am taught, therefore, that given a sensitive animal, the nature of its response to a toxic injection of tuberculo-protein will depend altogether on my method of introducing the antigen. If the preparation enters the body in such a way that it will get into the circulation rapidly, acute and fatal anaphylaxis will result. If it is absorbed more slowly, there will either be no symptoms or the symptoms will tend to approximate the comparatively gradual illness that occurs when we inject the tuberculous animal subcutaneously. It further seems as though we have to do with an antibody that is present in the circulation which reacts with the antigen to set free a powerful toxin—the so-called anaphylotoxin of Friedberger. In further support of this idea that the antibody that is concerned in the production of the acute anaphylaxis is free in the circulation, is the circumstance that in some forms of protein anaphylaxis, the serum of a sensitized animal will render a second animal sensitive to the particular protein if transferred to the latter.

After demonstrating that the non-tuberculous animal that had been treated with tuberculo-protein was unlike the normal animal but similar to the tuberculous animal in that it would react to very small amounts of this antigen, Baldwin showed further that a large proportion of tuberculous animals that had never before received tuberculo-protein would react to it exactly like the sensitized animals that were not tuberculous. If he injected such tuberculous animals subcutaneously or intraperitoneally with extract-emulsion, they would suffer the well-known general tuberculin reaction, which manifested itself several hours later and ended in death if the dose was sufficiently large. If, however, he introduced his extract-emulsion postorbitally, many of these tuberculous animals would die in a few minutes of acute anaphylaxis and would show the typical lesions of the heart and lungs. Not all tuberculous animals, picked at random, will react in this way and the reason why they differ from one another is not yet clear, but probably depends upon the nature and extent of the tuberculous foci, the conditions of absorption from them, and the animals' inherent ability to create antibodies. But after injecting say fifteen tuberculous guinea-pigs of one lot, I have had sixty per cent show acute anaphylaxis.

This event brought out plainly that all that was necessary to prove one point of similarity between tuberculous guinea-pigs and sensitized, non-tuberculous ones was to treat each kind with a toxic dose of antigen postorbitally—that is, in a rapidly absorbable way. The first logical deduction was that the tuberculous animal had a circulating anaphylactic antibody; another, that it was identical with that of the sensitized, non-tuberculous animal; a third, that it was produced in response to the same antigen as in the latter; and a fourth, that the antigen arose in the tuberculous focus and was probably the tubercle bacillus.

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After these relations had been worked out the first problem that naturally suggested itself was to find out what would happen to a non-tuberculous animal if it were treated with tuberculo-protein like tuberculous animals that are undergoing tuberculin therapy. The specific treatment of tuberculosis after a long period of disuse and even disrepute has of late years been gradually coming into its own again. Clinician after clinician is now taking up the method, and the majority of capable observers are reporting strikingly good results in many cases. However, the action of the bacillary preparations so far as their therapeutic uses are concerned still remains as mysterious as ever. Their application thus far has been purely empirical and limited only by the clinical judgment of the practitioner. The general opinion of the latter has been, I believe, that the introduction of carefully graded doses rouses the tuberculous organism to the overproduction of defensive substances—antibodies—that neutralize the poisons elaborated in the focus or attack the bacilli themselves or perform both of these functions.

The idea that the bacillary products that are ordinarily used contain primary toxins, does not seem tenable. If we had to do with such toxins, they should poison the normal, non-tuberculous as well as the tuberculous animal. But we have seen that extremely large doses are without untoward effect on the normal animals. If there are toxins, too, they should stimulate the animal organism to the production of antitoxin in amounts directly proportional to the quantity of tuberculo-protein introduced. As a matter of fact, no one has ever succeeded beyond dispute in producing an antitoxin to any derivative of the bacillus.

But how the picture changes when we consider animals that have already absorbed antigen! If an animal be infected experimentally it begins to react to tuberculin on or about the fifteenth day; in like manner, the non-tuberculous animal treated with protein will react to a second injection given about two weeks after the first. Both classes of animals will then be made violently ill by exceedingly small doses of the protein. What other explanation can we have but that in both there have been produced antibodies that react with antigen to set free a poison—the anaphylactic poison?

Nor do we have to assume that the tuberculous focus throws out toxins in order to explain the ordinary symptoms of the disease—the weakness, the anorexia, the tachycardia, the emaciation, the fever that are so often observed. Indeed it is more rational, in the light of our present knowledge, to ascribe these to the continual absorption of antigen by an already sensitized system. If an extract of the entire contents of several tubes of cultures of tubercle bacilli will not make a normal animal the least bit ill, why should the products of comparatively few bacilli, as many as would be enclosed in a tubercle the size of a walnut, bring about so severe an intoxication of an animal? It is hard to explain this on the toxin idea, but the conception of hypersensitiveness makes it much clearer.

The method of tuberculin therapy that is in most common use to-day is that of treating the individual with small doses and gradually raising them until the patient can tolerate quite large amounts without reaction. Every therapeutist comes to realize that there is no exact guide in this treatment and that his sole index in proceeding with tuberculin injections is the manner in which the patient responds to them. He finds that he cannot even predict which particular case will do well and which one will lose ground under treatment. He learns that so far as the results are concerned each individual patient is a law to himself; and that, if the latter holds his ground or improves, it is probably safe to continue with tuberculin, but if his health retrogrades it is better to discontinue it. Out of the tremendous mass of conflicting evidence that clinicians have given us, I think that several generalizations can fairly be made. These are that the chronic, afebrile case, who is in good condition and whose disease is not too far advanced, is the most favorable case for treatment; that such a patient's condition is often improved by tuberculin therapy after he has long ceased to show improvement under the other well-known methods of treatment; that those patients do best who can tolerate relatively large amounts of tuberculin, and conversely, those patients can best tolerate tuberculin who are most free from symptoms of their disease; and that in many cases the patient's tolerance to tuberculin is apparently greatly increased by spaced, gradually increasing doses of the antigen. And it is this latter principle—to diminish hypersensitiveness and its consequent intoxication—that has perhaps been the leading aim in therapy.

I therefore attempted to imitate the conditions of tuberculin therapy on non-tuberculous animals and to follow the results so far as sensitiveness was concerned. I wished to find out whether I could render them tolerant or immune to tuberculo-protein. In the experiment I used thirty-six normal guinea-pigs, which I divided into three sets of twelve each. Each set received spaced, gradually increasing amounts of water-extract at various intervals of time—one set every two days, another every four days, and a third every seven days. After they had reached fairly high dosage the animals were allowed to go without treatment for from seven to sixteen days, when they were given postorbital injections of extract-emulsion. The animals that were treated every two days began with 0.25 cc. W. E. subcutaneously and after thirty-nine days were getting 5 cc. intraperitoneally; those treated every four days began with 0.25 cc. subcutaneously and ended on the thirty-ninth day with 4 cc. intraperitoneally; those treated every seven days began with 0.25 cc. subcutaneously and ended on the thirty-ninth day with 4 cc. intraperitoneally. The first set received a total of 25 cc. W. E. in seventeen doses; the second, a total of 13 cc. in ten doses; the third, a total of 8 cc. in six doses. Seven days after treatment stopped, I tested several members of each series postorbitally, and again sixteen days afterwards. All of the animals except one were very sensitive to the ordinary toxic doses for sensitized guinea-pigs (0.75 cc. E. E.), while most of them reacted strongly to very small doses (0.15 cc. to 0.3 cc.). The general result was to indicate that after repeated doses sensitiveness was much greater than after single injections. There was no evidence that tuberculo-protein toleration could be obtained in non-tuberculous animals by repeated dosing,—there was, at least, no noticeable tolerance seven days after treatment stopped. A further endeavor was then made to discover whether there was any tolerance whatever for a very short time after regular treatment with the protein. I therefore repeated the experiment I have just cited, making the toxic, postorbital injection three days after the last subcutaneous treatment. I thus tested four animals and found them all sensitive, three of them fatally so. I have since treated many animals with more than a single sensitizing injection and have found that the best way to attain a very high degree of sensitiveness is to give them repeated injections of antigen—and that the larger the individual doses of antigen, the greater the degree of sensitiveness.

These experiments led to two conclusions; namely, first, once sensitiveness to tuberculo-protein is acquired by a non-tuberculous animal, the repeated absorption of protein tends only to increase this condition; and second, tolerance to tuberculo-protein cannot be attained in these animals by gradually raising the dosage or diminishing the intervals of time between doses. Other experiments, which I shall cite later, showed that perceptible sensitiveness persists for a long time after a single injection—often for more than a year—but that there is a tendency for it to diminish as time goes on unless it is renewed by further applications of antigen.

The results of the experiments which I have just described do not seem to square with the clinical idea of the method of gaining tolerance in the tuberculous, and it is this contradiction to which we must now address ourselves. As the first step, let us examine the nature of the different forms of sensitiveness as they exist in the tuberculous organism.

If we treat the skin with a derivative of the tubercle bacillus either by applying the latter to a break in the surface or injecting it between the layers of the skin, we find that some hours afterwards an inflammation will occur at the site of or in the immediate neighborhood of the injection. All of our present knowledge indicates that this inflammation is the ultimate result of an interaction between the injected antigen and antibodies that are present at the point of injection, and that

these antibodies are produced by the diseased organism in response to antigen that has arisen from the tuberculous focus. According to von Pirquet's view all of the cells of the body take part in this response to stimulation by antigen. At the Saranac laboratory we have never been able to elicit a skin reaction in guinea-pigs unless the animal has tubercles caused by living or dead bacilli; that is, a first injection of extracted protein will not sensitize to a later skin reaction. Moss, however, has found that individuals sensitized with horse serum acquire a skin sensitiveness to the serum. The possibility of sensitizing the skin by injecting an animal with pure tuberculo-protein is therefore not so remote if we once hit upon the proper conditions; and we are still working along this line.

If a small amount of tuberculo-protein enters the body subcutaneously or intraperitoneally or even intravenously (provided in the last instance that not too much anaphylactic antibody is present in the circulation) the tuberculous focus will suffer a reaction. This reaction also comes on several hours after the injection and expresses itself symptomatically by evidences of increased activity of the disease process, such as cough and expectoration in pulmonary tuberculosis, and anatomically by inflammation. As in the skin reactions, this inflammation is also most likely the end result of the union of antigen and anaphylactic antibody at the focus. Now the inflammation of the focus introduces a factor altogether different from any that can exist in the sensitized, non-tuberculous animal. By bringing about circulatory changes and softening the focus it renders the absorption of the focal material much easier than it was before. This focal material thrown rapidly into the circulation then reacts on an organism that has already been sensitized to it during the course of the disease and brings about an acute type of illness, the so-called general fever reaction, the manifestations of which are not at all unlike those met with in any acute exacerbation of the disease. Indeed, there is great similarity between what occurs during the general reaction and the course of events in ordinary acute tuberculosis. In both there are signs and symptoms of increased inflammatory focal changes: in both, the symptoms are very much alike. I have already said that the conception that the symptoms of tuberculosis are due to the absorption of focal material is more reasonable than the primary toxin idea; and it is evidence such as this that leads me to think that the general reaction is a phenomenon that depends upon what happens at the focus after a tuberculin injection. I am at the present time engaged in experiments in an attempt to discover what the sensitizing material of the focus is: whether it is the bacilli or the necrotic material or a substance that is formed by the effect of one acting on the other. My results are still very incomplete, but I may say here that I have not been able to confirm Kraus and Volk's observation that extracts of focal material are primarily toxic for guinea-pigs while those of normal organs are not.

Besides these three forms of reaction there is the so-called puncture reaction, which is essentially a local reaction and similar to the skin reactions, and the acute anaphylactic reaction, which we have already discussed.

Let us take such a tuberculous animal with local, focal and what I may call acute anaphylactic sensitiveness and wander into more or less hypothetical ground. If we should inject it subcutaneously with tuberculin we might get a puncture reaction and no other perceptible response to the injection. Here I should say that at the point of injection there was enough anaphylactic antibody present to bind all or most of the antigen, so that if there was a residuum of the latter it was not enough to combine with sufficient antibody to cause reaction elsewhere. Most of the protein would be neutralized, as it were, at the surface of the body. If, however, the peripheral antibody were absent, or small in amount, or if the doses were considerably larger than what the peripheral antibody could take care of, the antigen would get into the circulation. Here it would meet with circulating anaphylactic antibody if the latter were present. The acute anaphylactic shock would not result, however, because on account of slow absorption the units of antigen would be picked up one by one, and we have already seen that the fulminant symptoms are only brought on when we introduce the antigen in such a manner that it gets into the circulation very rapidly. Whatever antigen is bound by circulating anaphylactic antibody becomes incapable of reacting with the anaphylactic antibody in the focus and thus the focus is protected to a degree that is directly proportional to the amount of circulating antibody that exists at any one time. We should have here a very unusual condition. The circulating anaphylactic antibody would be a great menace to an animal if the antigen were injected intravenously, but it is just as great a bulwark against focal and general reactions if the antigen is so injected that absorption is slow. With the combination proceeding gradually unit by unit all the circulating antibody is used up without the production of symptoms, and the only way that the focus will be affected will be by the unbound residual antigen. Thus we should have two zones of defense, which I may call peripheral and circulating zones; and the contingency of a focal reaction would depend upon quantitative relations between peripheral and circulating antibody and antigen, as well as upon time relations that would govern the binding of the two opposing substances, which in turn would depend largely upon the method of injection and the degree of solubility of the antigen that is employed. I have approached this matter of absorption experimentally in the following manner. I first injected sensitized, non-tuberculous guinea-pigs with very large doses of extract-emulsion intraperitoneally and followed this up some time later with a post-orbital injection. When the second injection had been given some time (one-half to one hour and a half) after the first injection it very often failed to bring on the anaphylactic symptoms, showing that the circulating antibody had disappeared. These observations have been sufficiently controlled to be of some value, and I have experiments now under way in which I am trying to establish the time relations more definitely.

But there is a third defensive zone with which we have to do. This is of a mechanical nature and is comprised in the extent of fibrosis that any given tuberculous focus has undergone.

It seems to me that if a tubercle is well invested by fibrous tissue it can stand assaults by tuberculin much more successfully than if no such protection exists. As healing occurs, and more and more scarring takes place, and the tubercle becomes less and less vascular, it certainly must happen that less extraneous matter can be carried into the tubercle. This factor must surely be of prime importance in many cases. We know that as a general thing the longer a given case has been healed and the more completely a lesion has been closed in, the larger our dose of tuberculin must be to induce reactions. There are some exceptions to this rule but I believe the generalization can safely be made. Now the non-tuberculous animal, once sensitized, gradually loses this condition unless we inject more antigen—in other words, its circulating antibody diminishes in amount. The case that has been healed for a long time would so far be comparable to the former. We should assume, therefore, that it had less circulating anaphylactic antibody to protect its old focus. The tubercle, however, has a more or less efficient protection of its own, namely, its fibrous capsule.

We now begin tuberculin therapy with a tuberculous animal, such as we have been considering. If the tissues of the tuberculous animal respond to injections of tuberculo-protein like those of the non-tuberculous animal—and I see no reason why they should not—they will gradually heap up anaphylactic antibody in the circulation. If there is very little of this antibody to begin with, or if the focus is naked, as it were, with but slight fibrosis, we have manifestly a more delicate task ahead of us than if the reverse is the case. We can conceive of several possible conditions of the patient at the time he starts treatment. He may have much circulating antibody with a well invested tuberculosis, or much circulating antibody with more or less softened tubercles, or little circulating antibody combined with either focal condition. It is therefore not hard to foresee how every case may respond in its own way to tuberculin. But if we have a favorable case to begin with, the tendency would be, as stated, to stimulate the organism to the production of circulating antibody, which, as we have assumed, protects the focus against subsequent doses of antigen and is one of the factors in the so-called acquired tolerance after treatment. I now have experiments under way to test the validity of this hypothesis. By repeated doses of antigen I sensitized normal animals to a high degree. I have lately rendered these sensitive animals tuberculous, together with normal, non-sensitive control animals. In a couple of months, after the disease is well established, I shall give both sets lethal doses of tuberculo-protein subcutaneously or intraperitoneally. If my hypothesis is correct I shall expect to find the initially non-sensitive animals reacting focally to smaller doses than those that were sensitized before inoculation.

The other factor in the production of tolerance in therapy would enter in the direct action of the tuberculo-protein on the focus itself. Since we know that tuberculo-protein inflames the tubercle, it is more than likely that the end result of every dose that reaches the tubercle, no matter how small, is to bring about changes that may vary from the most transient hyperæmia to the most intense inflammation of the focus. It seems quite reasonable that slight inflammations could be of real service in assisting the healing process of the tubercle and many clinical observations, which it is unnecessary to go into here, support this view. Certainly by the increased stimulation of fibrous reaction the scarring process would be hastened. The amount of tuberculo-protein which would react with the focus would depend upon the conditions that I have already mentioned. With a good defense of circulating antibody the focus would pick out only the residual tuberculo-protein and would be saved from the dangers of too violent a reaction—the excessive inflammation and a dissemination of the disease that might result were the tubercle subjected to all the protein of a given dose. Hyperæmia and inflammations during the course of treatment might be so slight as to be imperceptible, yet their end effects—the resultant focal sclerosis—might be marked. And as the focus gradually becomes closed in during the healing process, the third zone of defense that we have considered would become strengthened and assist appreciably in producing tolerance to the antigen.

I think that you have already become impressed by the fact that the problems of the tuberculin reaction and of tuberculin therapy are extremely complicated ones and that any adequate theories of them must take into consideration a great many factors. In the above recital I have tried to do no more than elaborate a working hypothesis that is based on well authenticated clinical observations and on experimental work that has been carried on at the Saranac laboratory. I have tried to separate what has been demonstrated from what remains yet to be proved before these conceptions can be lifted from the realms of hypothesis to those of theory. And if I have been successful in suggesting fruitful paths of experimentation I shall be more than satisfied.

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A problem of the first importance is what relation the hypersensitiveness to the products of a given microörganism bears to susceptibility to infection from it. It has long been known that during the course of an infection the diseased individual becomes sensitive to the organic products of the infecting agent, but thus far we have had practically no experimental information concerning the part that the sensitive state plays in the defensive processes of the organism against bacillary implantation. It was our problem, therefore, to discover whether the tuberculo-protein sensitized animal acquired increased or lowered resistance to infection by the tubercle bacillus.

I accordingly undertook experiments in which I aimed, first, to sensitize normal animals; next, to inoculate these together with normal, non-sensitive controls; and finally, to sacrifice the whole number after the tuberculosis was well established and compare the progress of the disease in the initially sensitive animals with that in the control animals. The animals that I sensitized before inoculation comprised forty-two guinea-pigs which were divided into four sets. The members

of set A received a subcutaneous or intraperitoneal injection of water-extract every two days over a period of thirty-nine days in which they got a total of 25 cc. Those of set B were similarly treated every four days and received a total of 13 cc. in the thirty-nine days. Each animal of set C, treated every seven days, had in all 8 cc. during the thirty-nine days. The individuals of set D were given only one sensitizing injection,—1.25 cc. of water-extract intraperitoneally. There were originally twelve animals in set A, twelve in set B, twelve in set C and six in set D. Sixteen days after the preliminary treatment of sets A, B and C ended, I tested individuals from each lot and found that a high degree of sensitiveness to extract-emulsion existed in all of the tested animals. At the same time I gave two members of each set A, B and C sub-lethal doses. These last named animals all showed severe anaphylactic symptoms but did not die. I did not test the animals of set D, because I had sensitized animals in a similar manner many times previously and had always found them hypersensitive.

I was now ready for my inoculation. For this purpose I took six animals, that were sensitive but had not been tested, from each of the sets, A, B, C, and D; two from each of the sets A, B, and C that had received a toxic postorbital injection an hour before, had shown symptoms but had to a certain extent recovered from them; and six normal non-sensitized animals as controls. I thus had six different lots for inoculation, made up as follows: Lot 1, six guinea-pigs that had been sensitized, then given sub-lethal toxic injections, and were more or less intoxicated at the time of inoculation. These animals were in a refractory condition to further immediate injections of protein, since their first non-lethal toxic injection protected them against a second. Lot 2, six guinea-pigs, sensitized by treatment every two days, and not given toxic injections. Lot 3, six guinea-pigs, sensitized by treatment every four days, not given toxic injections. Lot 4, six guinea-pigs, sensitized by treatment every seven days, not given toxic injections. Lot 5, six guinea-pigs, sensitized by one injection thirty-seven days before inoculation. Lot 6, six normal untreated guinea-pigs.

I injected each of the above animals in the same spot subcutaneously in the right groin with one-tenth of a cubic centimeter of an emulsion of human tubercle bacilli prepared as follows: Several spadefuls of a beef serum culture were rubbed up in a mortar with a minimal amount of physiological salt solution until the mixture was a fairly homogeneous paste. This was then diluted and centrifugalized several times. The supernatant emulsion was pipetted off, further diluted and again centrifugalized. The resultant supernatant emulsion was then filtered several times through cotton. This filtrate was the final emulsion that was used for inoculation. Examination of the filtrate showed no clumps and an average of but one tubercle bacillus to every one or two fields of the oil immersion lens. Before inoculating each animal the beaker containing the stock emulsion was given the same number of whirls to ensure an even mixture and but one-tenth of a cubic centimeter was withdrawn at any one time.

Sixty-two days afterwards the animals were killed and their condition noted. The results of the inoculation can be summarized as follows:[2]

Refractory Animals, 5 guinea pigs.—Total weight at time of inoculation, 1795 grams; average weight, 369 grams; total weight, 62 days later, 2200 grams; average weight, 440 grams; average net gain, 81 grams. None pregnant. There is advanced tuberculosis in all. The lungs and spleen are involved in every animal, and the liver in two.

Sensitized Animals, treated every 2 days, 6 guinea pigs.—Total weight at time of inoculation, 2265 grams; average weight, 377 grams; total weight, 62 days later, 2690 grams; average weight, 448 grams; average net gain, 71 grams. Three were pregnant. The disease has reached the spleen in only one of the six and has advanced no further in any.

Sensitized Animals, treated every four days, 6 guinea pigs.—Total weight at time of inoculation, 2100 grams; average weight, 350 grams; total weight, 62 days later, 2650 grams; average weight, 442 grams; average net gain, 92 grams. Two were pregnant, one of which littered 31 days after inoculation. The spleen is involved in three of the six guinea pigs. The process has affected other viscera in only one which was pregnant and in which the lungs were diseased.

Sensitized Animals, treated every 7 days, 6 guinea pigs.—Total weight at time of inoculation, 2185 grams; average weight, 364 grams; total weight, 62 days later, 2950 grams; average weight, 492 grams; average net gain, 128 grams. Two were pregnant. The spleen was involved in three, and the lungs in two of these three.

Sensitized Animals, given only one dose, 6 guinea pigs.—Total weight at time of inoculation, 2140 grams; average weight, 357 grams; total weight, 62 days later, 2680 grams; average weight, 447 grams; average net gain, 90 grams. One was pregnant. The spleen was diseased in every animal and the lungs in two.

Control, Non-sensitized Animals, 6 guinea pigs, 5 autopsied.—Total weight at time of inoculation, 2180 grams; average weight, 436 grams; total weight 62 days later, 2830 grams; average weight, 566 grams; average net gain, 130 grams. None were pregnant. The spleen was involved in four of the five animals and the lungs in two.

So far as known, all of the pregnant animals became pregnant after inoculation. Macroscopic tuberculosis is meant in the above descriptions when an organ is said to be involved.

The refractory animals suffered most. The disease was pretty well disseminated in all of these and they exhibited far more tuberculosis than any of the animals that had not been intoxicated and than any of the controls. It will be remembered that these refractory animals were given toxic injections about an hour before inoculation. The widespread extent of the process was very likely due to the fact that the bacilli were implanted in animals that were still more or less poisoned at the moment of infection. And it would appear that the animal organism is less resistant to infection than normal during the period that it is undergoing symptoms of anaphylaxis or before it has completely recovered from their effects. Whether this event is specific or whether toxicity from one bacterio-protein would fail to render an animal more susceptible to infection by another microörganism is a matter that has not yet been determined. We know that some infectious diseases undoubtedly increase the susceptibility to tuberculosis: or, at any rate, that tuberculosis often actively

[2] Details of these experiments are to be found in an article in the Journal of Medical Research, 1911, XXIV, 2, 361.

appears during or after the course of another disease. It would be interesting and important to find out whether this diminished resistance to tuberculosis is due to the intoxication that is brought about by hypersensitiveness to another bacterio-protein, and I am now trying to solve this problem by experimentation.

The animals that were sensitized in various ways all became diseased. As a general thing, we may say that the more protein the animal received during preliminary treatment, the less the resultant infection. So far as I could tell from the toxic symptoms of the tested animals, there was very little difference in the average degree of sensitization between members of the several sets. Nevertheless, the reaction is a gross one and the mere fact that animals from three different series reacted fatally does not imply that their degree of sensitization is the same. You will easily see that if one thousand antibody units, say, or 0.3 cc. of antigen, were enough to produce death in a given guinea-pig, then ten thousand antibody units or 0.5 cc. of antigen would bring about the same result in another guinea-pig. Both die but are not equally sensitive, for guinea-pig B would have ten times as much antibody as guinea-pig A. We can, however, determine the degree of sensitiveness by graduating the dose of antigen which would be the constant. The guinea-pig would be the variable and its symptoms in response to a fixed, moderate dose of antigen would determine its sensitiveness. Unfortunately in these experiments I did not have enough animals to determine these variations. Since the preparation of an article that has lately been published and in which I assumed that the animals of the different series were probably equally sensitive, I have had occasion to deduce from a number of experiments that sensitiveness does fluctuate—tending to die out, though very slowly indeed, if the antigen is not renewed and being markedly increased by repeated injections. I am glad therefore to take this opportunity to qualify my former assumption and point out its fallacy.

However, it is very likely that the differences of tuberculous involvement were altogether independent of any degree of raised or lowered resistance conferred by the sensitive state, but that they were due to a heightened immunity that followed the protein injections and was brought about by other unknown factors. The changes that occurred in those guinea-pigs that had only one sensitizing dose support this view. These were inoculated thirty-seven days after sensitization. Experiments covering a period of two years have shown us that thirty-seven days after an intraperitoneal injection of 1.25 cc. of water extract, a guinea-pig is almost invariably fatally sensitive. So we are pretty safe in assuming that at the time of inoculation these were highly sensitive. Yet these "one dose" animals suffered in just about the same measure as did the controls. The one dose of water-extract was not sufficient to make them immune to infection. But it was enough to sensitize them, and while sensitive they contracted about as much tuberculosis as did the normal animals. This evidence would therefore strengthen the opinion that sensitization to a bacterio-protein of itself does not convey immunity to infection, and also that hypersensitiveness and increased resistance are probably two different phenomena. The experiment also shows definitely that they can exist side by side in the same animal.

But we must remember that in our experiments we have very likely introduced into the animal body relatively large amounts of the infecting agent compared to what is taken in under natural conditions of infection. It is conceivable that the degree of sensitiveness that would express itself by fatal anaphylaxis might confer upon the animal the capacity to get rid of ten or fifty or one hundred tubercle bacilli, numbers that probably represent the amount of infecting material that is naturally introduced more nearly than the number contained in our inoculated emulsion. The question is certainly an open one and the point must be emphasized. At the Saranac laboratory we are now employing the more exact method of Barber in our inoculation of sensitized animals. This as you know consists in counting out the living microörganisms one by one, and thus enables us to infect with any desired number from one up. By the use of this method we hope to determine definitely whether sensitization carries with it any increased resistance to infection.

* * * * * * * * *

There remains one phase of our work on sensitization which I should like to bring before you. This is the matter of the inheritance of tuberculo-protein sensitiveness. Most of you know that Rosenau and Anderson first demonstrated that sensitiveness to horse serum was transmitted from the female guinea-pig to its offspring and that the male parent has no influence in this transmission. Their work has been confirmed by Gay and Southard, Lewis, and Otto. Schenck has brought forward some evidence that serum sensitiveness may also to a slight degree be handed down from the male parent. In his work on tuberculo-protein anaphylaxis, Baldwin found that the law of maternal transmission also held good with this bacillary derivative. Guinea-pigs, the offspring of actively sensitized mothers, reacted when one or two months old.

Although Baldwin was unable to show in a few animals that the tuberculous mother, which has not been treated with tuberculo-protein, transmits sensitiveness to her young, the chances are in favor of the possibility that in some instances she actually does so. You will remember that a certain proportion of tuberculous animals react to postorbital injection of bacillary protein with acute anaphylaxis in exactly the same manner as non-tuberculous sensitized ones; and that the similarity of the reaction compelled the conclusion that the reaction is in both instances the resultant of the same factors; namely, an interaction of antigen and circulating antibody. Since therefore the non-treated tuberculous animal which will react and the treated, hypersensitive animal are in exactly the same anaphylactic condition which results from the same fundamental cause, it would seem certain that in some cases tuberculous females would bear offspring that are perceptibly sensitive. This would necessarily follow in an animal that would conceive and carry young to term during a period in which she herself had considerable circulating antibody and was very sensitive. Thus far in our laboratory we have come across no

sensitive offspring of tuberculous mothers, but we are still testing all such young, in the belief that sooner or later we shall encounter a sensitive guinea-pig.

There is probably no other disease that has occasioned so much discussion in regard to hereditary influences as tuberculosis, and any addition to our knowledge on this subject further than mere surmise is manifestly important. Baldwin's discovery of the maternal transmission of tuberculo-protein hypersensitiveness is, I believe, the first satisfactory evidence of the inheritance of any specific property in relation to tuberculosis. While we do not yet know what part the hypersensitive condition to bacterial products plays in immunity—whether it protects against natural infection or lays the animal organism more open to invasion—it seemed worth while to try to find out how constantly the tuberculo-protein sensitized mother will transmit the condition, and how long the animal that is born sensitive will retain the anaphylactic state. Because, too, of the logical inference, as outlined above, that under certain conditions tuberculous mothers must confer a sensitiveness on their offspring that may be perceptible or imperceptible, I thought it well to continue Baldwin's experiments.

I tested a total of sixty-one young, giving them single post-orbital or intravenous injections of extract-emulsion. All were the offspring of presumably sensitive mothers which were not tuberculous. When they were tested they varied greatly in age as well as in the time that had elapsed between the mother's last dose of antigen and the birth of the different animals. I shall not burden you with the details of the experiments, which may be found in another publication, but shall merely state their results, which may be summed up as follows:

1. The possibility of maternal inheritance is more or less irregular and inconstant.

2. It depends largely on the degree of sensitiveness of the mother at the time of pregnancy.

3. The degree of sensitiveness of the offspring as a rule varies directly with that of the mother.

4. The mother's sensitiveness is heightened by repeated applications of antigen, and, conversely, tends to die out with time unless renewed by subsequent injections.

5. The degree of sensitiveness of the offspring accordingly varies, depending on the time that has elapsed between the mother's last dose and the birth of the offspring.

6. The degree of sensitiveness that an animal inherits tends to diminish as it increases in age and size.

7. Guinea-pigs have been born sensitive 379 days after their mother's last injection of antigen. They have also remained sensitive as long as 404 days after birth, although they had never been tested before.

8. Animals of the same litter may vary greatly in the degree of sensitiveness which they inherit.

9. The fact that a number of animals were born sensitive over a hundred days, and several 379 days, after their mothers' last injection, is direct evidence that the transmission may be one of anaphylactic antibody and not of the antigen.

10. The transmission by inheritance is probably always or mainly one of antibodies.

11. Hypersensitiveness to tuberculo-protein is most likely never handed down to the third generation. This conclusion is based on tests on nine animals, the grandchildren of sensitized females through the female line.

All this evidence concerning inheritance will probably be of more tangible value after we find out what rôle hypersensitiveness plays in infection. Meanwhile it furnishes encouragement for more experimentation in this direction.

In the above recital of experimental work performed and in the discussion of where such investigations lead, I have done little more than state the problem of tuberculo-protein hypersensitiveness in its relation to several of the phases of tuberculous infection. I thank you heartily for the forbearance with which you have followed me, and trust that the future will bring forth still more fruitful results than the past.

VARIATIONS IN THE LEUCOCYTE COUNT IN NORMAL RABBITS, IN RABBITS FOLLOWING THE INJECTION OF NORMAL HORSE SERUM, AND DURING A CUTANEOUS ANAPHYLACTIC REACTION.

By W. L. Moss, M. D.,
Associate in Medicine, Johns Hopkins University.

AND

G. L. Brown, M. D.,
Research Worker.

(From the Research Laboratory, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital, Baltimore, Md.)

The observations to be reported in this paper were made in connection with some recent work of Knox, Moss and Brown (The Journal of Experimental Medicine, 1910, XII, No. 4) on a local anaphylactic reaction in rabbits. Healthy rabbits were sensitized by the intravenous injection of normal horse serum in doses of 0.1 cc. to 5 cc. After an interval of 12 days or longer their sensitiveness was tested by an intradermal injection of 0.01 cc. normal horse serum given in the skin of the abdomen. A positive reaction consists of localized inflammation and swelling, varying from 0.5 cm. to 2 cm. in diameter which appears within 24 hours and usually subsides in three or four days.

In connection with this work we attempted to determine if the total or differential leucocyte counts underwent any characteristic changes either following the sensitizing injection or during the local anaphylactic reaction produced by the intradermal injection of 0.01 cc. horse serum.

A considerable number of observations have been published on changes in the leucocytes following the injection of various antitoxic sera and during the anaphylactic reaction in human beings, a very good summary of which appears by Bianco Bienenfeld (Jahrbuch für Kinderheilkunde und Physiche Erziehung, N. F., Bd. LXV, 1907). Bienenfeld's personal observations showed a leucopenia, immediately following the injection of large doses of serum, followed by a leucocytosis, which, in most cases of the serum disease, in turn gave place to a recurrence of leucopenia. The leucopenia is ascribed to negative chemotaxis and is characterized by a diminution of the polymorphonuclear neutrophiles. The non-granular cells seem much more resistant to these changes than do the granular cells, since they undergo much less diminution. The eosinophiles are not affected. Bienenfeld states that toward the end of the leucopenia there appear many large mononuclear and transitional cells. These are ascribed to regenerative processes in the blood and lead to the belief that during the serum disease there is destruction of leucocytes followed by regeneration; however, owing to lack of more positive proof, the author leaves the question open as to the cause of the leucopenia, whether it is due to non-functionating of the blood-forming organs or to a destruction of leucocytes.

Hamburger and v. Reuss (Ueber die Wirkung artfremden genuinen Eiweisses auf die Leukozyten. Zeitschrift für Biologie, 1910, XLVII, 24) in a large series of experiments carried out on rabbits found that the intravenous injection of foreign proteids is followed in about five minutes by a marked diminution in the number of leucocytes. An exception to this rule was found in the case of horse serum which caused practically the same result as the injection of homologous (rabbit) serum, namely, a hyperleucocytosis. The same result, hyperleucocytosis, followed the injection of normal salt solution and indeed simple venepuncture without any injection. The authors consider the hypoleucocytosis following the injection of foreign proteid, the result of a toxic action.

Aschenheim (Ueber Schwankungen der Leukocytenzahle nach Traumen und Injektionen. Zeitschrift für Biologie, 1910, LI, 385) injected a series of rabbits with homologous and heterologous serum and in opposition to Hamburger and v. Reuss observed hypoleucocytosis following the homologous, as well as the heterologous serum. Simple venepuncture, without injection of any kind, was followed by hyperleucocytosis. Aschenheim was unable to refer the effect on the leucocyte count of simple venepuncture to reflex vasomotor changes due to painful stimuli; since anesthesia did not prevent the occurrence of hyperleucocytosis. He admits, however, that his experiments were not conclusive since the sympathetic system may not have been inactive under anesthesia.

Subcutaneous injections into human beings of human serum and serum from a variety of animals, produced changes in the leucocyte count which followed no definite rule.

In the light of our own experience, which did not come until after many counts had been made, we feel that in none of the work which we have seen reported, has enough care been bestowed upon the establishment of the variations in the normal leucocyte counts in rabbits. It was not until after we had obtained many confusing results that we devoted our attention seriously to this point.

Before giving the results of our counts a brief description of the conditions under which the work was carried out will be given.

Young adult rabbits about a year old and of approximately the same size and weight were selected from a large number of country-raised rabbits. The males were separated from the females throughout the experiments and no pregnant females were used.

In the first series tested, as many as four or five rabbits were kept in a three- by four-foot cage, but in the subsequent series each rabbit was kept in a separate cage in order to prevent fighting, which might result in injuries or infections and thus influence the leucocytes.

All rabbits were fed once a day at approximately the same hour, 10 a. m. The food consisted of greens, grain and hay in such quantity that all would usually be consumed in four to six hours after feeding.

The blood for counting was taken from an ear vein and to insure a free flow of blood, after the ear was shaved, cleaned with alcohol and dried, a test tube containing warm water was placed beneath the ear; this caused a prompt dilatation of the veins and free flow of blood. As soon as the pipette for counting had been filled, smears for the differential counts were made.

Thoma-Zeiss blood counting apparatus was used; the pipettes were of the large, 1-20 dilution variety, the diluent was prepared fresh each day by adding four drops of glacial acetic acid to 40 cc. distilled water. In all cases two slides of five square millimeters each were counted in order to determine the total number of leucocytes.

The films for the differential counts were stained with Hastings' stain and a total of 200 cells counted for each differential. Duplicate counts made in a number of instances showed that this number of cells gave percentages which agreed quite closely with those given by counting 400 cells or more.

Since the value of this work depends entirely upon the accuracy of the counts we have attempted to get some idea of the percentage error in our counts. To this end we made duplicate determinations at frequent intervals throughout the work. A free flow of blood having been obtained from the ear vein, two pipettes were filled in rapid succession and two slides of five square millimeters each counted from each pipette. The average percentage variation of the two counts from the mean of the two counts in 48 such duplicate determinations was 7.5 per cent.

We further tried to get an idea of the accuracy of the counts by determining the percentage variation of each slide from the average of the two slides. In 174 such determinations the average percentage variation between slides was 3.9 per cent.

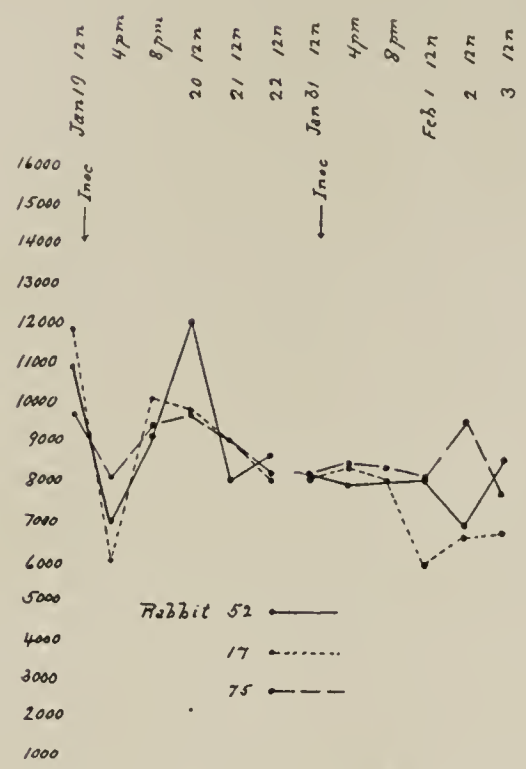

CHART I.—TOTAL LEUCOCYTE COUNTS.

Jan. 19 injected normal horse serum intravenously as follows: Rabbit No. 52, 0.1 cc.; Rabbit No. 17, 1 cc.; Rabbit No. 75, 5 cc. Jan. 31 injected 0.01 cc. normal horse serum intradermally in all three rabbits.

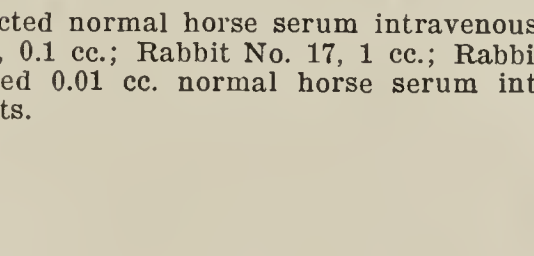

CHART II.

Rabbit No. 52 showing total leucocyte count and absolute values for polymorphonuclear, large and small mononuclear leucocytes.

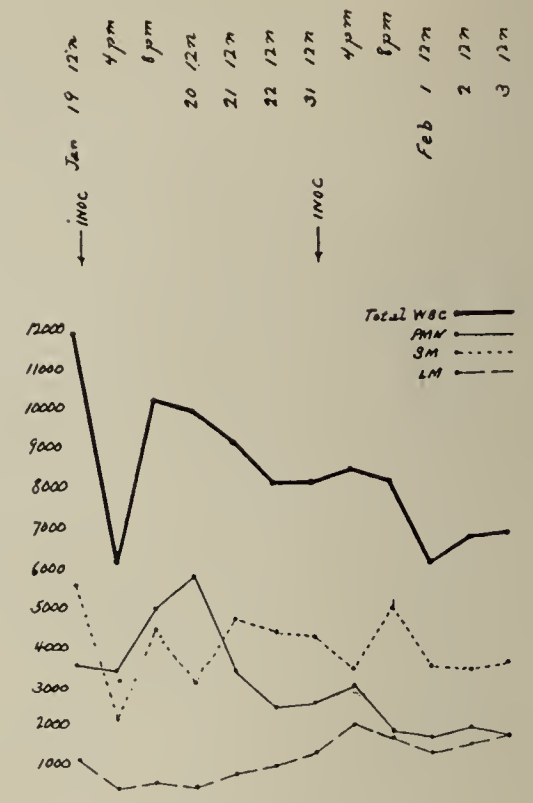

CHART III.

Rabbit No. 17 showing total leucocyte count and absolute values for polymorphonuclear, large and small mononuclear leucocytes.

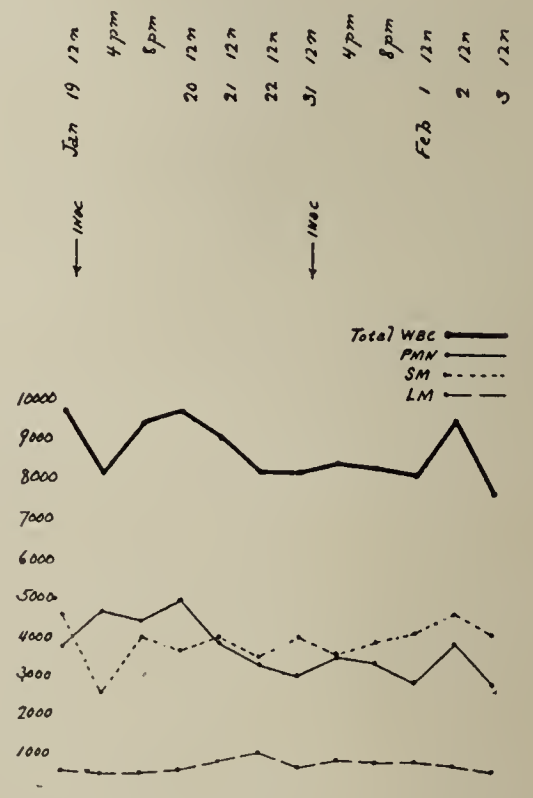

CHART IV.

Rabbit No. 75 showing total leucocyte count and absolute values for polymorphonuclear, large and small mononuclear leucocytes.

On two occasions we filled three pipettes in rapid succession from the same rabbit and twice we filled five pipettes. The results of the counts made from the separate pipettes are tabulated below:

	Rabbit No. 23, March 14, 1910	Rabbit A	Rabbit No. 99, May 19, 1910	Rabbit No. 99, May 20, 1910
1st pipette	8670	7360	4100	3540
2d pipette	8660	7880	4020	4060
3d pipette	8470	7720	3920	3560
4th pipette			4220	4060
5th pipette			3780	3700
Average	8600	7653	4008	3784
Greatest variation from average	1.5%	3.8%	5.4%	7.3%

The above percentages represent all the data we have on the accuracy of the counts and we feel they indicate that our results may be taken as trustworthy.

FIRST SERIES.

Rabbit No. 52. January 19, 1910, injected 0.1 cc. normal horse serum intravenously. January 31, 1910, cutaneous anaphylactic test, 0.01 cc. normal horse serum intradermally. Local reaction negative.

	Total Leucocytes	Pmn* %	Pmn* Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
Before injection	10900	22.5	2452	15.0	1635	57.5	6268	3.5	381	1.5	164
4 hours after	7000	47.4	3318	6.6	462	39.4	2758	4.0	280	2.4	168
8 " "	9100	55.6	5060	6.3	574	32.6	2966	1.6	146	3.6	328
24 " "	12000	32.3	3876	6.0	720	57.6	6912	1.3	156	2.6	312
48 " "	8000	27.0	2160	5.5	440	63.0	5040	2.5	200	2.0	160
72 " "	8600	27.6	2373	14.3	1230	52.0	4477	4.0	344	2.0	174
Before test	8200	52.3	4287	9.4	771	35.0	2870	1.5	124	1.6	132
4 hours after	7900	36.6	2892	8.6	680	51.3	4053	2.6	206	0.6	48
8 " "	Lost	42.8	..	9.2	..	45.2	..	1.6	..	1.2	..
24 " "	8000	22.0	1760	11.0	880	64.3	5144	0.3	24	2.3	184
48 " "	6900	25.0	1725	15.0	1035	55.5	3829	1.5	104	3.0	207
72 " "	8500	25.0	2125	14.0	1190	57.0	4845	4.0	340	..	..

Rabbit No. 17. January 19, 1910, injected 1.0 cc. normal horse serum intravenously. January 31, 1910, cutaneous anaphylactic test, 0.01 cc. normal horse serum intradermally. Local reaction doubtful.

	Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
Before injection	11800	29.8	3517	9.0	1062	46.9	5535	9.4	1110	4.7	555
4 hours after	6100	54.6	3331	5.0	305	34.0	2074	5.3	324	1.0	61
8 " "	10100	48.3	4879	4.6	465	43.0	4343	3.0	303	1.0	101
24 " "	9800	58.3	5714	3.6	353	30.6	2999	3.6	353	3.6	353
48 " "	9000	36.3	3267	7.6	684	51.0	4590	4.0	360	1.0	90
72 " "	8000	29.6	2368	10.4	832	53.2	4256	3.2	256	3.6	288
Before test	8000	30.6	2448	14.3	1144	51.6	4128	1.3	104	2.0	160
4 hours after	8300	34.3	2847	21.3	1770	39.0	3237	2.3	191	3.0	249
8 " "	8000	20.0	1600	18.0	1440	60.4	4832	0.8	64	0.8	64
24 " "	6000	24.0	1440	18.0	1080	55.2	3312	0.8	48	2.0	120
48 " "	6600	25.5	1683	19.5	1287	49.5	3267	3.0	198	2.5	165
72 " "	6700	21.5	1440	22.5	1508	51.0	3417	1.5	100	3.5	235

Rabbit No. 75. January 19, 1910, injected 5.0 cc. normal horse serum intravenously. January 31, 1910, cutaneous anaphylactic test, 0.01 cc. normal horse serum intradermally. Local reaction positive.

	Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
Before injection	9700	38.7	3753	5.7	552	46.7	4529	7.0	679	1.8	174
4 hours after	8100	57.3	4641	6.0	486	32.0	2592	4.0	324	0.7	56
8 " "	9400	46.6	4380	5.6	526	42.3	3976	4.6	432	0.7	65
24 " "	9700	51.0	4947	6.0	583	38.2	3705	3.2	310	1.5	145
48 " "	9000	42.6	3834	9.0	810	44.6	4014	3.0	270	0.6	54
72 " "	8200	40.0	3280	13.0	1066	43.0	3526	2.0	164	2.0	164
Before test	8200	37.2	3050	8.8	722	49.2	4035	1.6	131	3.2	262
4 hours after	8400	42.4	3562	10.8	907	43.2	3629	0.8	67	2.8	235
8 " "	8300	40.8	3386	10.0	830	46.8	3884	1.6	133	0.8	66
24 " "	8100	35.6	2884	10.4	842	52.0	4212	0.4	32	1.6	130
48 " "	9500	41.0	3895	8.0	760	49.0	4655	..	..	2.0	190
72 " "	7700	36.0	2772	7.5	578	53.3	4104	1.3	100	1.9	147

The variations which the leucocytes have undergone are more readily seen if the above figures are plotted out in the form of curves. Chart I shows the total leucocyte count for the three rabbits. Four hours after the intravenous inoculation of normal horse serum the leucocyte count had fallen in all the rabbits. The greatest drop is in rabbit No. 17, which received 1 cc. serum; the next greatest drop is in No. 52 which received 0.1 cc. serum; while the leucocytes of No. 75, which received 5 cc. serum, showed the smallest drop. Eight hours after the inoculation the leucocytes of all three rabbits had risen but not to their original levels. At the end of 24 hours the leucocytes of No. 52 slightly exceeded their original level and from this point on to the end of 72 hours all of the curves fell.

Following the intradermal injection of 0.01 cc. serum there was practically no change in the total leucocyte counts at the end of four and eight hours, in any of the rabbits. At the end of 48 hours the leucocytes of No. 75 were slightly increased. This rabbit was the only one of the series which gave a well marked positive reaction.

Charts II, III and IV show the total leucocyte count, the total number of polymorphonuclears, small and large mononuclears plotted out separately for each rabbit. It is evident from these three charts that the low leucocyte counts, four hours after inoculation, are due to a fall in the small mononuclears; this fall being great enough to bring the total count down in spite of a slight increase in the polymorphonuclears in the case of Nos. 52 and 75. In the case of No. 52, eight hours after inoculation the increase in the total count is due largely to an increase in the polymorphonuclears, while the still further increase in the total count at the end of 24 hours is due to a recovery of the small mononuclears which elements carry the curve to its high point in spite of a falling off of the polymorphonuclears at this time. There seems to be nothing noteworthy about the differential counts following the intradermal inoculation.

SECOND SERIES.

Rabbit No. 15 1910	Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
March 2, 9 a. m.	10195	36.0	3670	8.5	866	52.5	5352	1.0	102	2.0	204
1 p. m.	9965	36.0	3587	11.5	1145	47.5	4733	0.5	50	4.5	448
5 p. m.	11490	40.0	4596	7.0	804	47.5	5457	..	..	5.5	631
3, 9 a. m.	9875	28.0	2765	9.0	888	57.5	5678	1.0	99	4.5	434
4, 9 a. m.	9520	29.0	2760	10.0	952	57.0	5426	..	..	4.0	380
5, 9 a. m.	11090	32.5	3604	8.0	887	51.5	5711	3.5	388	4.5	499
March 16, 9 a. m.	10400	40.22	4191	16.88	1755	36.88	3836	..	..	6.0	624
1 p. m.	12580	31.0	3899	11.0	1383	51.5	6478	0.5	63	6.0	754
5 p. m.	12800	51.5	6592	10.0	1280	32.5	4160	0.5	64	5.5	704
17, 9 a. m.	11280	33.0	3722	9.5	1071	53.5	6034	..	..	4.0	451
18, 9 a. m.	9800	35.5	3479	10.5	1029	48.0	4704	1.0	98	5.0	490
19, 9 a. m.	9560	32.5	3107	11.0	1051	50.0	4780	1.0	95	5.5	525
March 21, 9 a. m.	9580	30.5	2922	12.0	1149	52.5	5029	..	..	5.0	479
1 p. m.	9860	38.0	3746	11.0	1084	47.0	4634	..	..	4.0	394
5 p. m.	9060	28.5	2582	16.0	1449	53.5	4847	0.5	45	1.5	136
22, 9 a. m.	6520	27.5	1793	11.25	733	55.75	3635	..	..	5.5	358
23, 9 a. m.	9880	31.0	3062	4.5	444	60.5	5977	0.5	49	3.5	345
24, 9 a. m.	11660	31.0	3614	4.5	524	60.0	6996	..	..	4.5	524
April 6, 9 a. m.	9920	39.0	3868	12.0	1190	45.5	4513	..	..	3.5	347
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	14460	46.5	6724	4.0	578	45.5	6579	..	..	4.0	578
5 p. m.	15200	22.5	3420	6.5	988	68.5	10412	..	..	2.5	380
7, 9 a. m.	11100	41.0	4551	13.5	1490	41.0	4551	..	..	4.5	499
8, 9 a. m.	10300	27.0	2781	6.0	618	64.0	6592	..	..	3.0	309
9, 9 a. m.	9700	41.5	4025	14.5	1406	39.5	3831	..	..	4.5	436
Rabbit No. 24											
March 2, 9 a. m.	5905	..	..	..	..	..	..	..	..	..	..
1 p. m.	8360	39.0	3269	13.5	1128	44.0	3678	0.5	41	3.0	250
5 p. m.	7990	29.5	2357	9.0	719	56.5	4514	0.5	40	4.5	359
3, 9 a. m.	5620	27.5	1545	15.0	843	56.5	3175	..	..	1.0	56
4, 9 a. m.	6290	24.0	1569	11.0	692	61.0	3837	..	..	4.0	251
5, 9 a. m.	5590	34.5	1928	7.5	419	55.5	3102	..	..	2.5	139
March 16, 9 a. m.	8880	20.5	1820	13.5	1198	56.0	4972	4.0	355	6.0	532
1 p. m.	10660	35.2	3752	12.8	1364	44.0	4690	4.4	469	3.6	383
5 p. m.	10220	37.0	3781	10.5	1073	42.0	4292	4.5	460	6.0	613
17, 9 a. m.	7140	22.4	1599	16.0	1142	54.4	3884	5.6	400	1.6	114
18, 9 a. m.	7500	33.5	2512	9.5	712	52.0	3900	3.0	225	2.0	150
19, 9 a. m.	7160	32.0	2291	12.0	859	50.0	3580	3.0	214	3.0	214

*In all the tables the following abbreviations are used:
Wbc=white blood cells.
Pmn=polymorphonuclears.
Lm=large mononuclears.
Sm=small mononuclears.
Eos=eosinophiles.
Mst=mast cells.

Rabbit No. 24—Cont.

	Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
March 21, 9 a. m.	6300	12.0	756	16.0	1008	65.0	4095	3.5	220	3.5	220
(Inoc. 0.01 cc. serum intravenously.)											
1 p. m.	7500	35.5	2662	13.0	975	43.5	3262	1.0	75	7.0	525
5 p. m.	8680	47.0	4079	8.0	694	38.5	3341	3.0	260	3.5	303
22, 9 a. m.	5900	27.5	1622	12.0	708	56.0	3304	0.5	29	4.0	236
23, 9 a. m.	5320	27.0	1436	5.5	292	59.5	3164	3.0	159	5.0	266
24, 9 a. m.	5820	30.5	1775	9.5	553	51.5	2997	3.0	174	5.5	329
April 6, 9 a. m.	7100	27.0	1917	5.5	390	62.0	4402	2.0	142	3.5	248
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	7660	44.0	3370	8.0	612	42.5	3255	1.5	115	4.0	309
5 p. m.	8940	30.5	2726	3.0	268	64.5	5766	1.0	89	1.0	89
7, 9 a. m.	6760	41.0	2771	5.5	372	51.0	3447	2.0	135	0.5	34
8, 9 a. m.	5680	34.0	1931	7.5	426	52.0	2953	4.0	227	2.5	142
9, 9 a. m.	7000	45.5	3185	7.5	525	41.0	2870	2.0	140	4.0	280
Rabbit No. 92											
March 2, 9 a. m.	7580	57.0	4320	8.5	644	33.5	2539	..	..	1.0	76
1 p. m.	9635	51.5	4962	9.0	867	38.0	3661	1.0	96	0.5	48
5 p. m.	9670	63.5	6140	6.0	580	26.5	2562	..	..	4.0	387
3, 9 a. m.	6840	61.0	4172	6.5	444	31.5	2154	..	..	1.0	68
4, 9 a. m.	11160	51.5	5747	6.5	725	40.0	4464	1.0	111	1.0	111
5, 9 a. m.	11310	76.0	8595	2.5	282	19.5	2205	0.5	56	1.5	169
March 16, 9 a. m.	6240	48.0	2995	9.0	561	37.0	2308	1.5	93	4.5	280
1 p. m.	8040	34.5	2773	10.0	804	52.5	4221	0.5	40	2.5	201
5 p. m.	6880	46.5	3199	9.0	619	42.0	2889	..	..	2.5	172
9 a. m.	7600	35.0	2660	13.5	1026	50.5	3838	..	..	1.0	76
17, 9 a. m.	9540	27.0	2576	9.5	906	60.5	5772	0.5	48	2.5	238
18, 9 a. m.	6460	56.5	3650	4.5	290	36.5	2358	0.5	32	2.0	129
March 21, 9 a. m.	6740	37.0	2494	9.5	640	52.0	3505	0.5	33	1.0	67
(Inoc. 1.0 cc. serum intravenously.)											
1 p. m.	6220	41.5	2581	6.5	404	48.0	2985	1.5	93	2.5	155
5 p. m.	7440	56.0	4166	6.0	446	35.5	2641	..	..	2.5	186
22, 9 a. m.	6780	42.0	2847	11.0	746	44.5	3017	..	..	2.5	169
23, 9 a. m.	8260	39.0	3221	8.0	661	50.5	4171	..	..	2.5	206
24, 9 a. m.	6260	30.0	1878	4.0	250	61.0	3819	0.5	31	4.5	282
April 6, 9 a. m.	6920	33.5	2318	4.5	311	62.0	4290	..	..	..	..
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	10060	53.0	5332	5.5	553	40.0	4024	0.5	50	1.0	100
5 p. m.	7940	36.5	2898	2.5	198	60.0	4764	0.5	40	0.5	40
7, 9 a. m.	6300	52.0	3276	10.5	661	34.5	2173	0.5	32	2.5	158
8, 9 a. m.	8360	45.0	3762	8.0	669	45.5	3804	0.5	42	1.0	83
9, 9 a. m.	5320	34.0	1809	5.0	266	58.5	3112	0.5	26	2.0	106
Rabbit No. 104											
March 2, 9 a. m.	7880	37.0	2915	8.5	670	51.5	4058	..	..	3.0	236
1 p. m.	10650	40.5	4313	6.0	639	49.0	5218	1.0	106	3.5	372
5 p. m.	10340	36.0	3722	11.5	1189	46.0	4756	..	..	6.5	672
3, 9 a. m.	7460	56.0	4177	4.0	298	37.0	2760	..	..	3.0	223
4, 9 a. m.	7160	33.5	2398	6.0	429	55.5	3974	0.5	36	4.5	322
5, 9 a. m.	9000	30.5	2745	6.5	585	58.5	5265	1.5	135	3.0	270
March 16, 9 a. m.	8860	25.5	2259	8.0	709	57.5	5094	1.0	88	8.0	709
1 p. m.	11160	42.0	4687	7.5	837	42.0	4687	5.5	613	3.0	334
5 p. m.	13480	35.5	4785	12.5	1685	45.5	6133	2.5	337	4.0	539
17, 9 a. m.	8760	33.0	2891	8.0	701	50.0	4380	4.5	394	4.5	394
18, 9 a. m.	12180	37.0	4506	10.5	1279	41.5	5054	3.0	365	8.0	974
19, 9 a. m.	10380	35.5	3685	12.0	1245	39.0	4048	8.5	882	5.0	519
March 21, 9 a. m.	5900	22.0	1298	14.5	855	55.5	3274	3.0	177	5.0	295
(Inoc. 5.0 cc. serum intravenously.)											
1 p. m.	9480	66.0	6256	4.5	426	26.5	2512	1.5	142	1.5	142
5 p. m.	7700	46.5	3580	7.5	577	37.5	2887	7.5	577	1.0	77
22, 9 a. m.	9020	36.5	3292	11.5	1037	46.5	4194	3.0	270	2.5	225
23, 9 a. m.	7940	45.0	3573	10.5	833	38.5	3057	1.0	79	5.0	394
24, 9 a. m.	8520	41.5	3535	11.0	937	39.0	3322	0.5	42	8.0	684
April 6, 9 a. m.	6280	38.5	2417	10.0	628	44.5	2794	1.0	62	6.0	376
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	10960	70.0	7672	2.5	274	24.5	2685	0.5	54	2.5	274
5 p. m.	10640	60.5	6437	2.0	212	34.5	3670	0.25	26	2.75	292
7, 9 a. m.	9200	58.0	5336	8.0	736	32.5	2990	0.5	46	1.0	92
8, 9 a. m.	8820	32.0	2822	8.0	705	56.0	4939	..	..	4.0	353
9, 9 a. m.	8040	35.5	2854	4.0	321	56.5	4542	1.0	80	3.0	241

Chart V represents the total leucocyte counts for the four rabbits of the third series plotted out in such a way that one can compare the variations in the whole series at a glance. This chart shows that the variations in the leucocytes during the two periods of observation before inoculation, March 2-5 and March 16-19 were approximately as great as those following the intravenous injection of serum, March 21, and the cutaneous test, April 6, except in the case of rabbit No. 15, which was a control and did not receive the intravenous inoculation with the others on March 16. This is made clear by the following figures:

	Two periods of observation before inoculation		Following intravenous inoculation*	Following intradermal inoculation
	Mch. 2-5	Mch. 16-19	Mch. 21-24	Apr. 6-9
Rabbit No. 15:				
Highest count..	11490	12800	11660	15200
Lowest count..	9520	9560	6520	9700
Variation	1970	3240	5140	5500
Rabbit No. 24:				
Highest count..	8360	10660	8680	8940
Lowest count..	5620	7140	5320	5680
Variation	2740	3520	3360	3260
Rabbit No. 92:				
Highest count..	11310	9540	8260	10060
Lowest count..	6840	6240	6220	5320
Variation	4470	3300	2040	4740
Rabbit No. 104:				
Highest count..	10650	12180	9480	10960
Lowest count..	7160	8760	5900	6280
Variation	3490	3420	3580	4680

This chart (V) shows in all cases an increase in the leucocytes at the count made either three hours or seven hours after feeding, with a fall by the next morning at 9 o'clock to somewhere near the original level. It seems quite reasonable to regard this increase as a digestive leucocytosis. The effect, if any, of the intravenous injection of serum, March 21, and the intradermal inoculation, April 6, is to depress to a slight extent the height of this digestive leucocytosis.

Charts VI, VII, VIII and IX represent the total number of leucocytes and absolute values of the polymorphonuclear, large, and small mononuclear leucocytes for rabbits Nos. 15, 24, 92 and 104, respectively. These charts show that in general an increase in the total leucocyte count is due to an increase in the two principal elements, the polymorphonuclear and small mononuclear leucocytes. In this series however, the polymorphonuclears as a rule undergo a greater increase than do the small mononuclears.

In order to determine if there is anything characteristic in the differential count following the intravenous injection of fairly large amounts of serum or the intradermal injection of minimal amounts we have analyzed the changes in the total counts and the number of polymorphonuclears and small mononuclears three hours and seven hours after injection. For purposes of comparison we have included the corresponding counts made before injection. The results are shown in the accompanying table, examination of which shows that an increase in the total count after the injection of serum may be due to an increase of either or both of the principal leucocytes and that this relationship does not differ from that entering into increases in the total count which occurred before the injection of any serum.

* Rabbit No. 15 was a control and did not receive an intravenous injection.

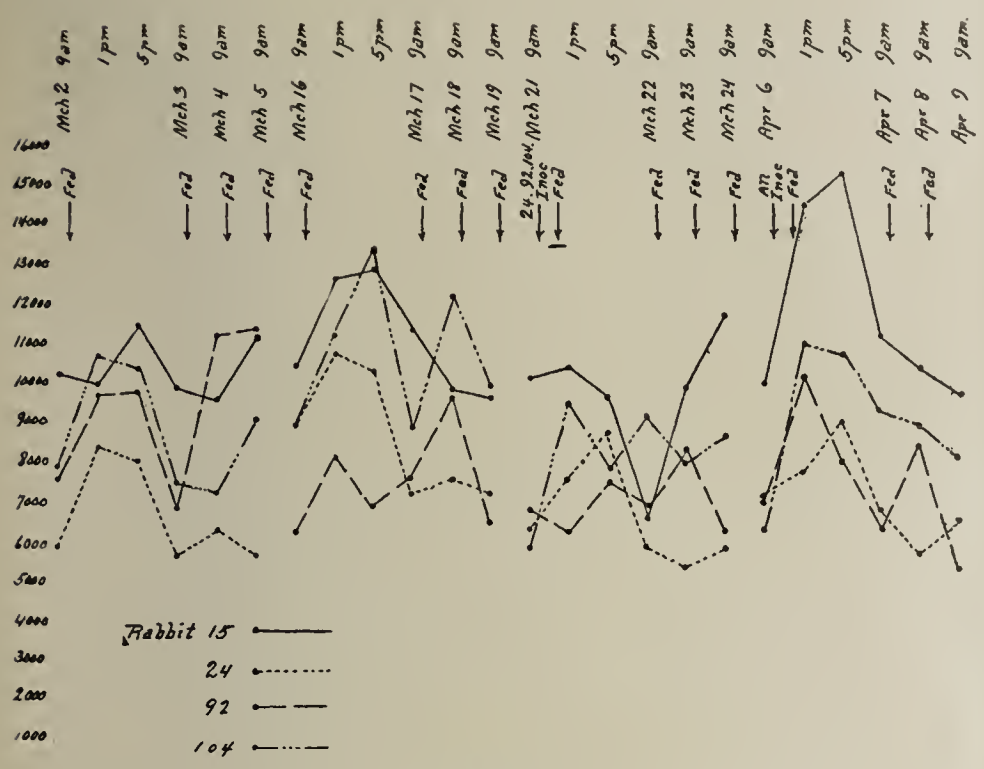

CHART V.

Rabbits Nos. 15, 24, 92 and 104 showing total leucocyte counts for entire period of observation. March 21 injected normal horse serum intravenously as follows: Rabbit No. 24, 0.1 cc.; Rabbit No. 92, 1 cc.; Rabbit No. 104, 5 cc. April 6 injected 0.01 cc. normal horse serum intradermally in all rabbits.

CHART VI.

Rabbit No. 15 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation. April 6, 10 a. m., injected 0.01 cc. normal horse serum intradermally.

CHART VII.

Rabbit No. 24 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

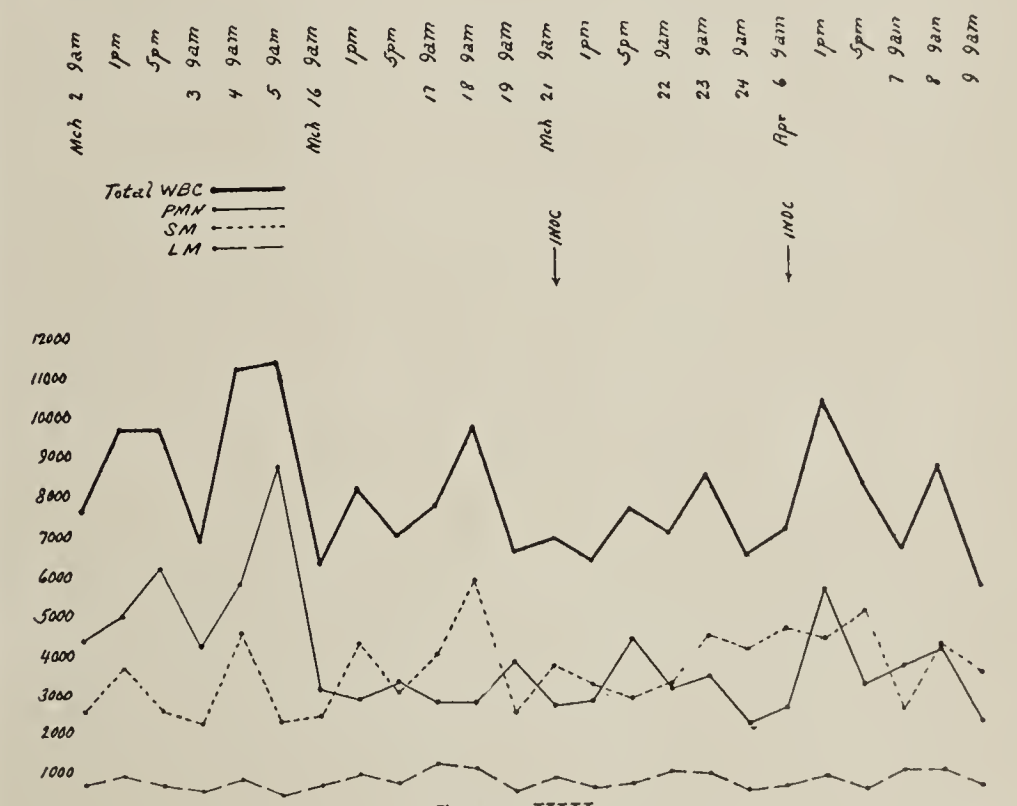

CHART VIII.

Rabbit No. 92 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

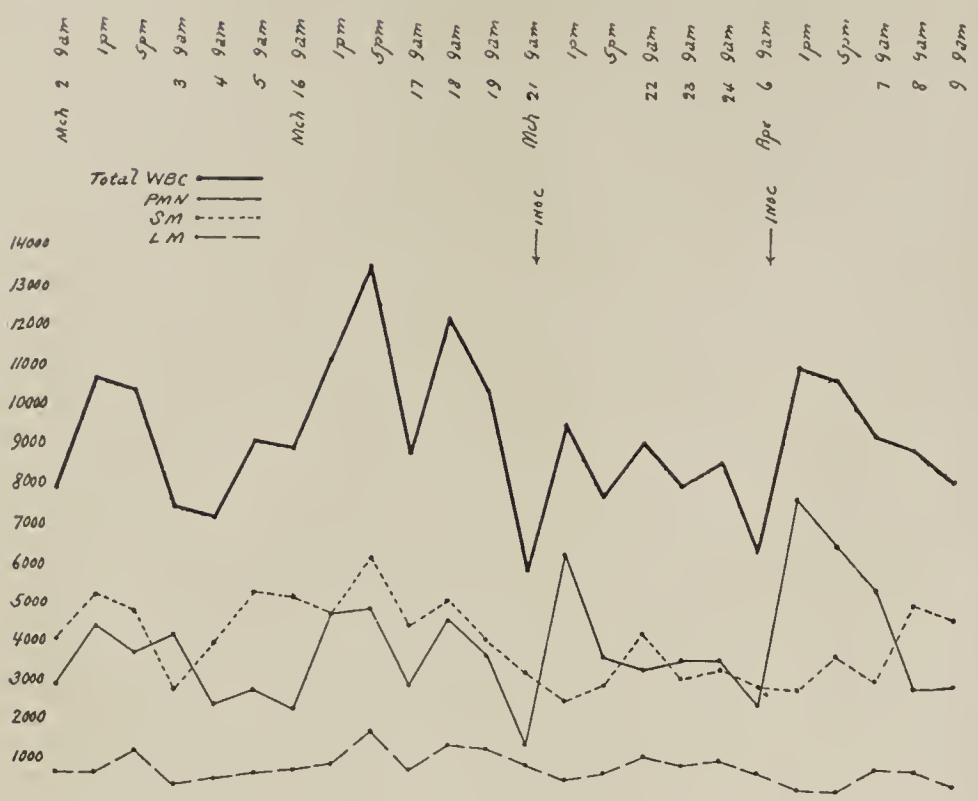

CHART IX.

Rabbit No. 104 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

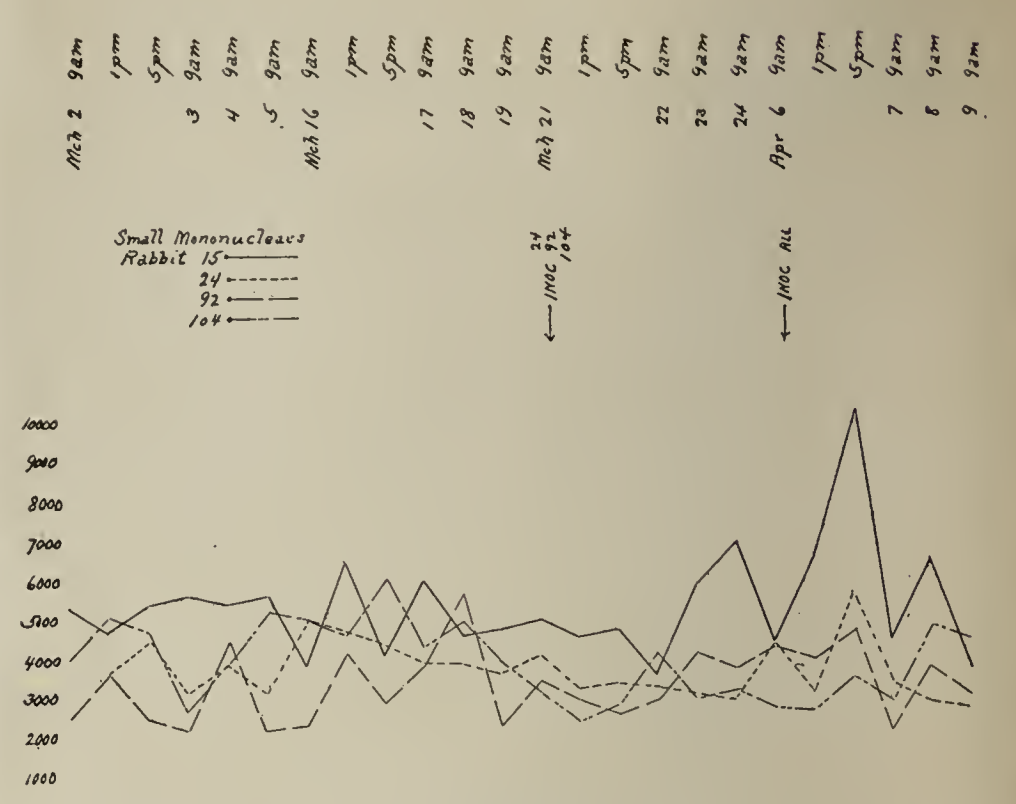

CHART XI.

Rabbits Nos. 15, 24, 92 and 104 showing absolute values of small mononuclear leucocytes.

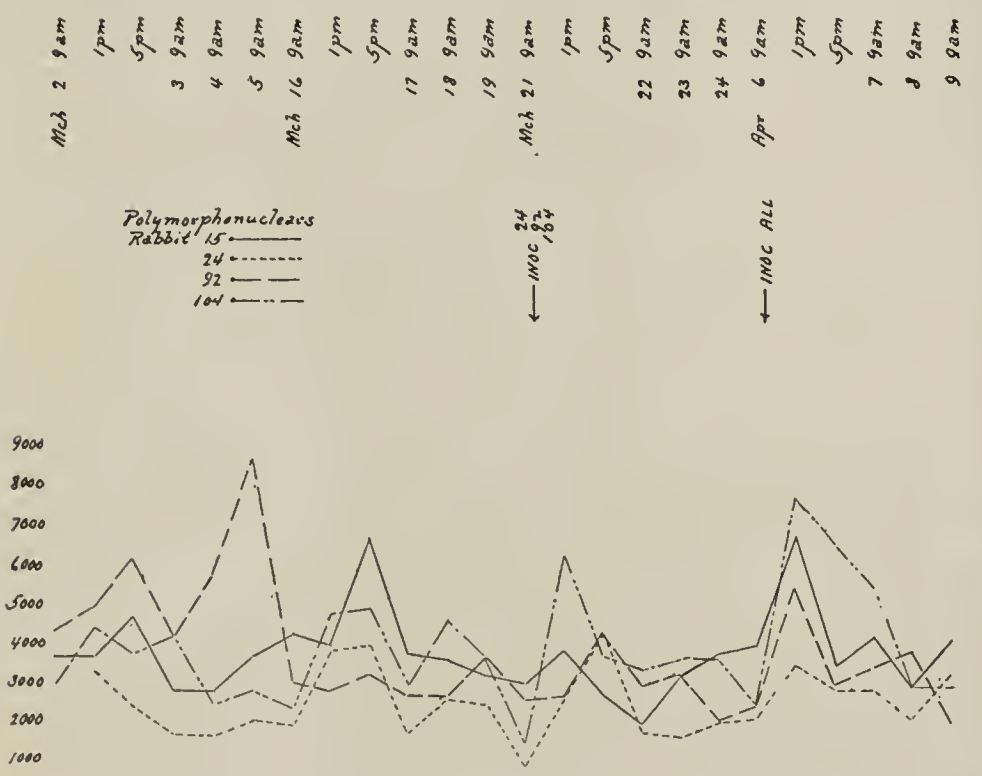

CHART X.

Rabbits Nos. 15, 24, 92 and 104 showing absolute values of polymorphonuclear leucocytes.

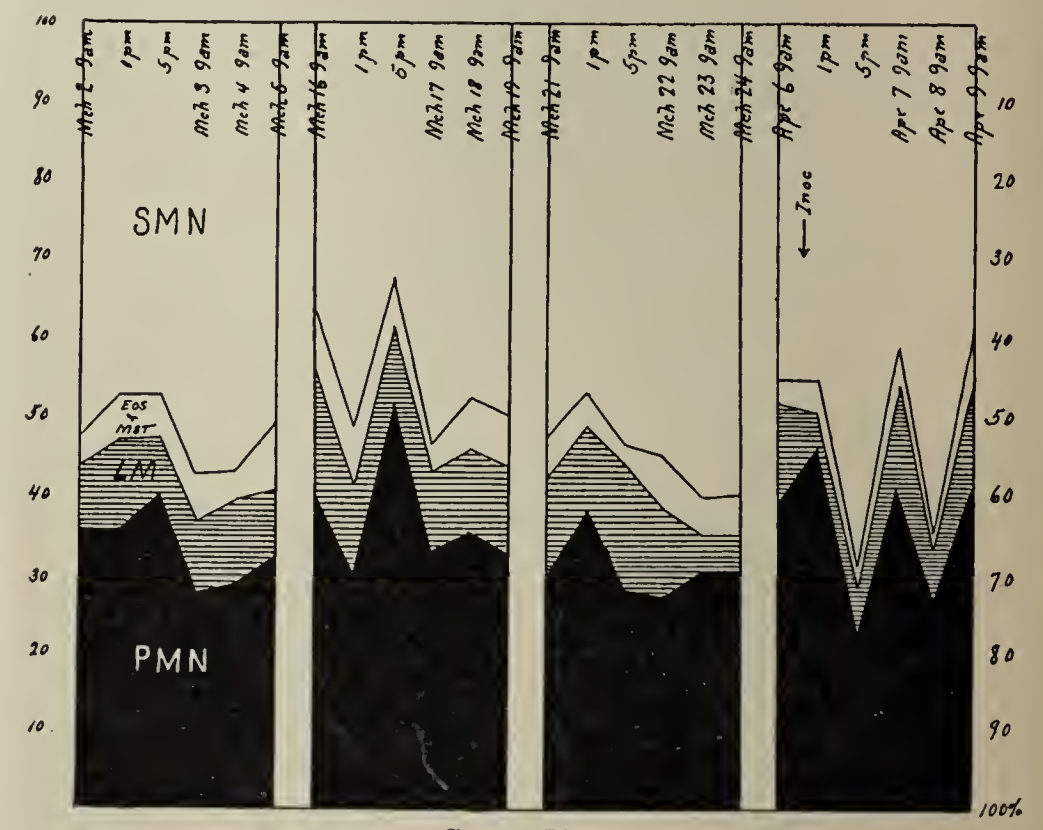

CHART XII.

Rabbit No. 15 showing percentage values of polymorphonuclear, large mononuclear, eosinophiles and mast cells combined, and small mononuclear leucocytes for entire period of observation.

	Two periods of observation before inoculation				Following intravenous inoculation*		Following intradermal inoculation	
	March 2		March 16		March 21		April 6	
	1 p. m.	5 p. m.	1 p. m.	5 p. m.	1 p. m.	5 p. m.	1 p. m.	5 p. m
Rabbit No. 15:								
Total leucocytes.	—	+	+	+	+	—	+	+
Pmn	○	+	—	+	+	—	+	—
Smn	—	+	+	—	—	+	+	+
Rabbit No. 24:								
Total leucocytes.	+	—	+	—	+	+	+	+
Pmn		—	+	+	+	+	+	—
Smn		+	—	—	—	○	—	+
Rabbit No. 92:								
Total leucocytes.	+	○	+	—	—	+	+	—
Pmn	+	+	—	+	+	+	+	—
Smn	+	—	+	—	—	—	—	+
Rabbit No. 104:								
Total leucocytes.	+	—	+	+	+	—	+	—
Pmn	+	—	+	+	+	—	+	—
Smn	+	—	—	+	—	+	—	+

+ denotes an increase over the preceding count.
— denotes a decrease from the preceding count.
○ denotes no change from the preceding count.

For the purpose of better comparing the changes in the polymorphonuclear and small mononuclear counts, we have prepared Charts X and XI in which their curves have been superimposed. Chart X shows a definite rise in the polymorphonuclears of all rabbits three hours after the intradermal inoculation of 1/100 cc. serum; this rise, however, was participated in by rabbit No. 15, which had not been previously injected, as well as by the others which had been injected intravenously on March 21. Chart XI shows nothing remarkable except the sharp rise in the mononuclears of rabbit No. 15 on April 6 at 5 p. m., which we are unable to explain.

Charts XII, XIII, XIV, XV, show the percentage values of the differential counts on rabbits Nos. 15, 24, 92 and 104, respectively. The black areas at the bottom of the charts represent the percentage of polymorphonuclears; the shaded areas, the large mononuclears; the unshaded areas at the top of the charts, the small mononuclears; while the unshaded areas between the small and large mononuclears represent the eosinophiles and mast cells combined. These charts show that the relative numbers of large mononuclears, eosinophiles and mast cells do not undergo great variations, and that the relationship between the polymorphonuclears and small mononuclears is, in general, a reciprocal one; that is an increase in the percentage of polymorphonuclears is accompanied by a decrease in the percentage of small mononuclears and *vice versa.*

It is important to realize the different impression one gets from a consideration of the differential count expressed in percentages and in absolute values. To illustrate, suppose a total leucocyte count of 8000 cells, of which the polymorphonuclears are 60 per cent, small mononuclears 30 per cent, large mononuclears, eosinophiles, and mast cells combined 10 per cent. Now imagine the total count to increase to 10,000 cells due to an increase in the polymorphonuclears of 2000 cells. The percentage values now change to 68 per cent for the polymorphonuclears, 24 per cent small mononuclears, and 8 per cent mononuclears, eosinophiles and mast cells combined. How little idea one could get of the real change from a consideration of the percentages alone can be seen from this example;

W. B. C. 8000	Pmn	60%	= 4800
	Sm	30	= 2400
	Lm, Eos and Mst.....	10	= 800
W. B. C. 10000	Pmn	68%	= 6800
	Sm	24	= 2400
	Lm, Eos and Mst.....	8	= 800

In order to confirm the results of the preceding series we ran through a third series, consisting of rabbits Nos. 105, 106, 107 and 108. Of these No. 105 served as a control and received on sensitizing injection; the remaining three received intravenous injections of normal horse serum on June 16 at 10 a. m. as follows:

Rabbit No. 106 1.0 cc. serum.
Rabbit No. 107 2.5 cc. serum.
Rabbit No. 108 5.0 cc. serum.

The total and differential counts are given in the following tables:

THIRD SERIES.

Rabbit No. 105 1910	Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
May 23, 9 a. m.	9900	26.5	2623	3.5	347	60.5	5989	4.5	446	5.0	495
1 p. m.	12140	28.5	3460	4.0	485	65.0	7891	1.5	182	1.0	121
5 p. m.	12900	27.5	3547	3.5	451	63.5	8191	2.0	258	3.5	451
24, 9 a. m.	9780	32.0	3129	5.0	489	59.0	5770	1.5	146	2.5	244
25, 9 a. m.	9080	22.0	1997	6.0	545	66.0	5993	2.0	181	4.0	363
26, 9 a. m.	8020	21.5	1724	5.5	441	69.0	5534	2.0	160	2.0	160
June 1, 9 a. m.	7540	21.0	1583	5.0	377	71.5	5391	1.0	75	1.5	113
1 p. m.	10320	24.5	2528	11.5	1187	62.0	6398	..	..	2.0	206
5 p. m.	11340	23.0	2608	5.5	624	70.0	7938	..	..	1.5	170
2, 9 a. m.	10500	16.0	1680	7.0	735	71.5	7507	..	..	5.5	577
3, 9 a. m.	9420	22.0	2072	2.5	235	71.5	6735	0.5	47	3.5	330
4, 9 a. m.	10600	20.0	2120	5.0	530	72.5	7685	..	..	2.5	265
June 16, 9 a. m.	7720	36.0	2779	6.0	463	56.5	4362	0.5	38	1.0	77
1 p. m.	6980	39.5	2757	5.5	384	53.0	3699	..	..	2.0	139
5 p. m.	8000	33.0	2640	2.5	200	61.0	4880	..	..	3.5	280
17, 9 a. m.	7940	26.5	2104	3.0	238	65.0	5161	0.5	40	5.0	397
18, 9 a. m.	6800	21.5	1462	5.0	340	71.5	4862	..	..	2.0	136
19, 9 a. m.	5300	26.5	1404	6.0	318	66.5	3524	..	..	1.0	53
June 29, 9 a. m.	8660	21.5	1861	4.0	346	69.0	5975	1.0	87	4.5	390
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	10250	27.0	2819	3.0	313	65.5	6838	1.0	104	3.5	365
5 p. m.	11260	38.5	4335	4.5	507	55.0	6193	..	..	2.0	225
30, 9 a. m.	9540	31.5	3005	5.0	477	59.5	5676	..	..	4.0	382
July 1, 9 a. m.	8560	25.5	2183	5.0	428	65.5	5607	1.0	85	3.0	257
2, 9 a. m.	7440	33.5	2492	2.5	186	62.0	4613	..	..	2.0	149
Rabbit No. 106											
May 23, 9 a. m.	4920	27.5	1353	7.5	369	64.0	3148	..	..	1.0	49
1 p. m.	7140	29.5	2106	10.5	749	58.0	4141	..	..	2.0	143
5 p. m.	7200	23.0	1656	9.0	648	67.0	4824	..	..	1.0	72
24, 9 a. m.	6100	11.0	671	4.5	274	81.0	4941	2.5	152	1.0	61
25, 9 a. m.	5580	29.5	1646	11.0	614	55.5	3097	0.5	28	3.5	195
26, 9 a. m.	4660	21.0	978	12.0	559	62.5	2912	0.5	23	4.0	186
June 1, 9 a. m.	6060	22.5	1363	14.0	848	56.0	3393	0.5	30	7.0	424
1 p. m.	8720	37.5	3270	6.5	557	51.0	4447	..	..	5.0	436
5 p. m.	6560	36.0	2361	10.5	689	45.5	2985	..	..	8.0	825
2, 9 a. m.	6720	31.5	2117	10.5	706	51.0	3427	..	..	7.0	470
3, 9 a. m.	4360	32.0	1395	5.0	218	55.5	2420	..	..	7.5	327
4, 9 a. m.	4360	47.5	2071	6.0	262	38.0	1657	1.0	43	7.5	327
June 16, 9 a. m.	4040	28.5	1151	7.0	283	55.5	2242	0.5	20	8.5	343
(Inoc. 1.0 cc. serum intravenously.)											
1 p. m.	8300	47.5	3942	4.5	373	45.0	3735	..	..	3.0	249
5 p. m.	6440	30.5	1964	7.0	451	59.5	3832	..	..	3.0	193
17, 9 a. m.	3800	33.5	1273	6.5	247	54.0	2052	0.5	19	5.5	209
18, 9 a. m.	4760	45.5	2166	10.5	500	39.0	1836	..	..	5.0	238
19, 9 a. m.	4920	39.0	1919	7.0	344	48.0	2361	..	..	6.0	295
June 29, 9 a. m.	5580	47.5	2650	7.0	390	40.0	2232	1.5	83	4.0	223
(Inoc. 0.01 cc. serum intradermally.)											
1 p. m.	6460	37.0	2389	6.5	420	55.5	3585	..	..	1.0	65
5 p. m.	6250	33.0	2062	10.5	656	46.0	2875	1.0	63	9.5	594
30, 9 a. m.	6780	44.5	3017	10.5	712	35.5	2407	1.0	68	8.5	576
July 1, 9 a. m.	7380	37.5	2767	8.5	627	47.0	3469	1.5	111	5.5	406
2, 9 a. m.	4720	40.0	1888	6.5	307	49.0	2313	0.5	23	4.0	189
Rabbit No. 107											
May 23, 9 a. m.	4600	38.5	1771	13.0	598	44.0	2024	..	..	4.5	207
1 p. m.	7480	29.5	2206	12.5	935	52.0	3889	..	..	6.0	449
5 p. m.	9440	27.5	2596	10.5	991	56.5	5333	0.5	47	5.0	472
24, 9 a. m.	4440	24.5	1088	13.0	577	60.0	2664	..	..	2.5	111
25, 9 a. m.	5580	29.0	1618	14.0	781	55.0	3069	..	..	2.0	112
26, 9 a. m.	5840	32.5	1898	11.0	642	50.0	2920	..	..	6.5	380

* Rabbit No. 15 served as a control and did not receive intravenous inoculation.

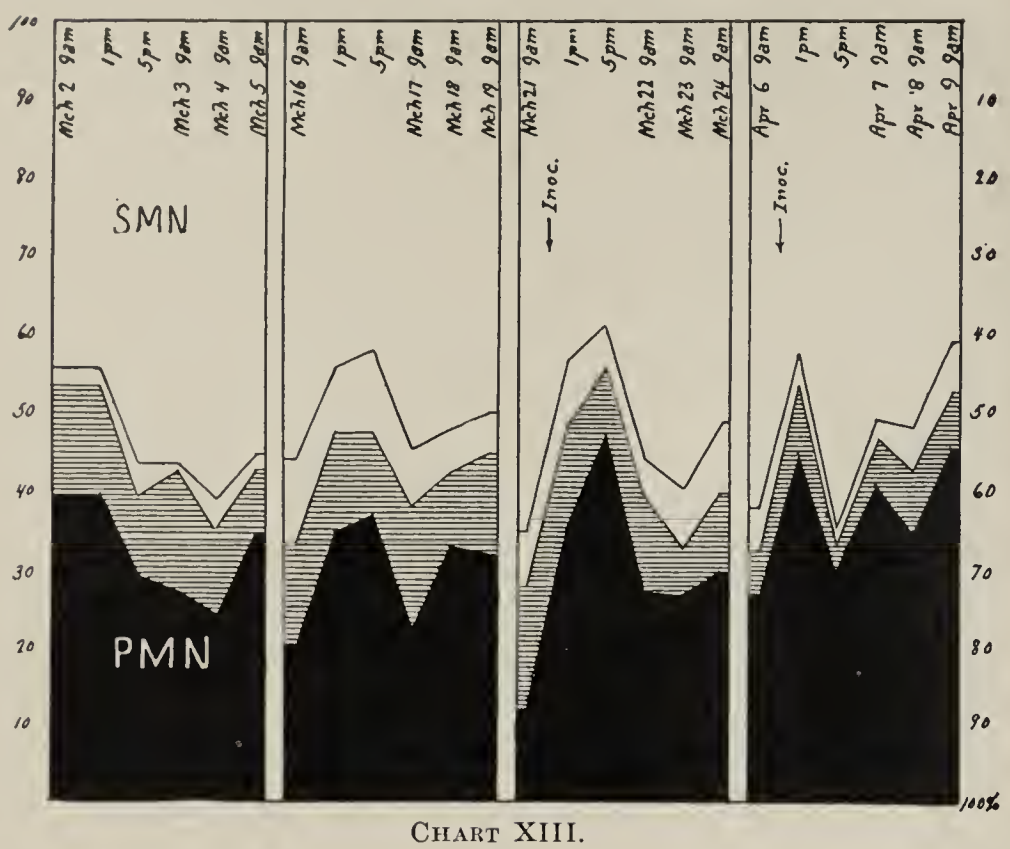

CHART XIII.

Rabbit No. 24 showing percentage values of polymorphonuclear, large mononuclear, eosinophiles and mast cells combined, and small mononuclear leucocytes for entire period of observation.

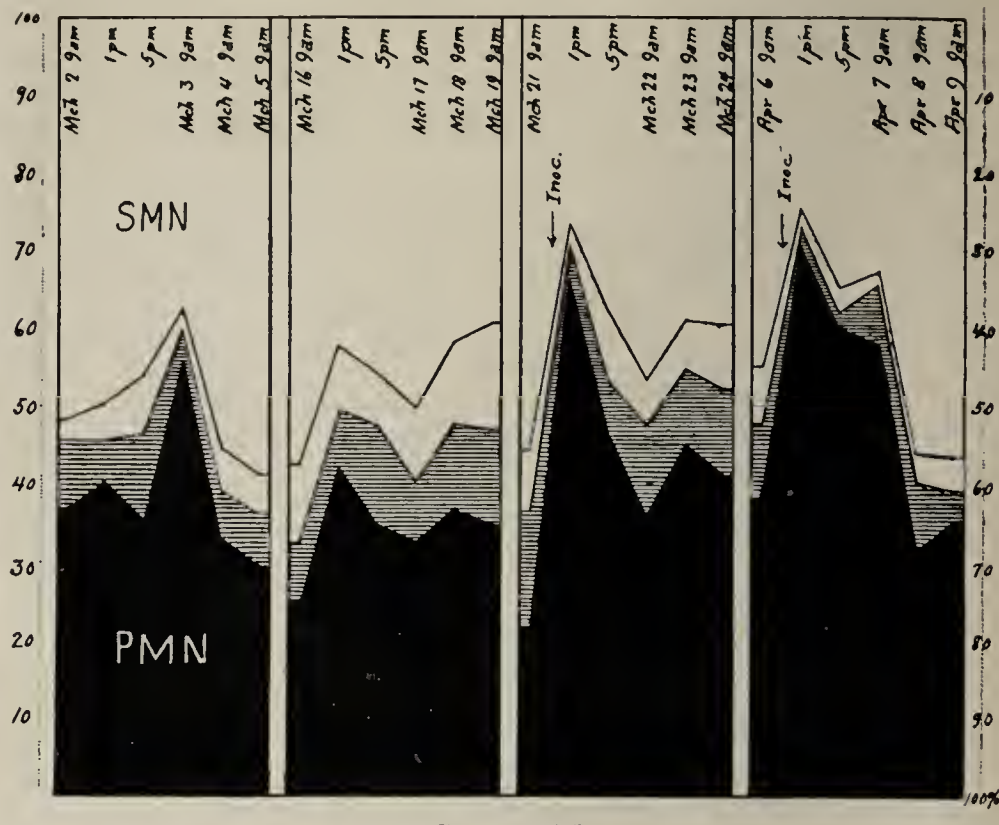

CHART XV.

Rabbit No. 104 showing percentage values of polymorphonuclear, large mononuclear, eosinophiles and mast cells combined, and small mononuclear leucocytes for entire period of observation.

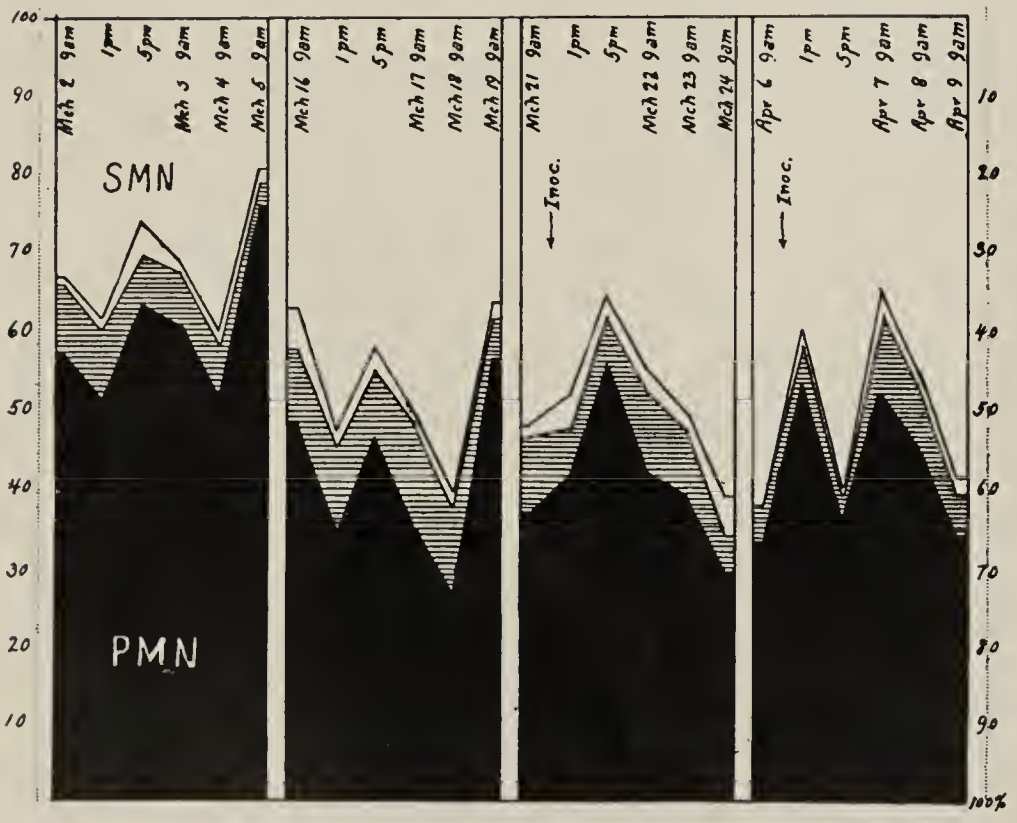

CHART XIV.

Rabbit No. 92 showing percentage values of polymorphonuclear, large mononuclear, eosinophiles and mast cells combined, and small mononuclear leucocytes for entire period of observation.

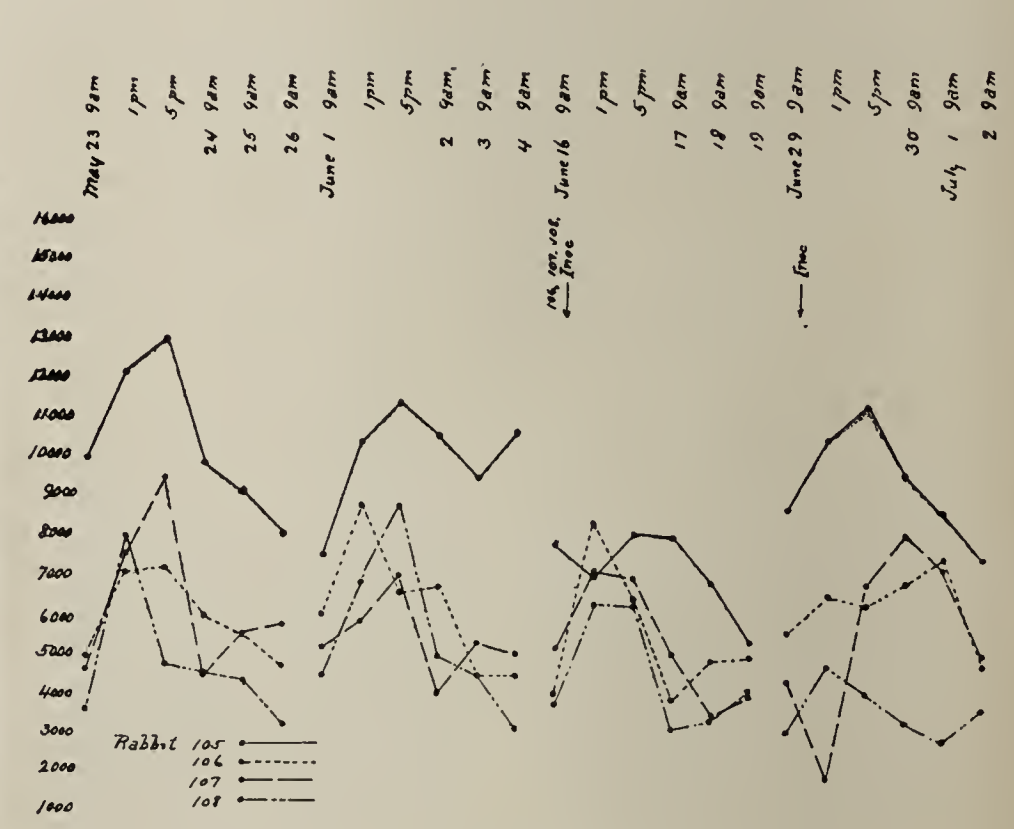

CHART XVI.

Rabbits Nos. 105, 106, 107 and 108 showing total leucocyte counts for entire period of observation. June 16 injected normal horse serum intravenously as follows: Rabbit No. 106, 1 cc.; Rabbit No. 107, 2.5 cc.; Rabbit No. 108, 5 cc. June 29 injected 0.01 cc. normal horse serum intradermally in all rabbits.

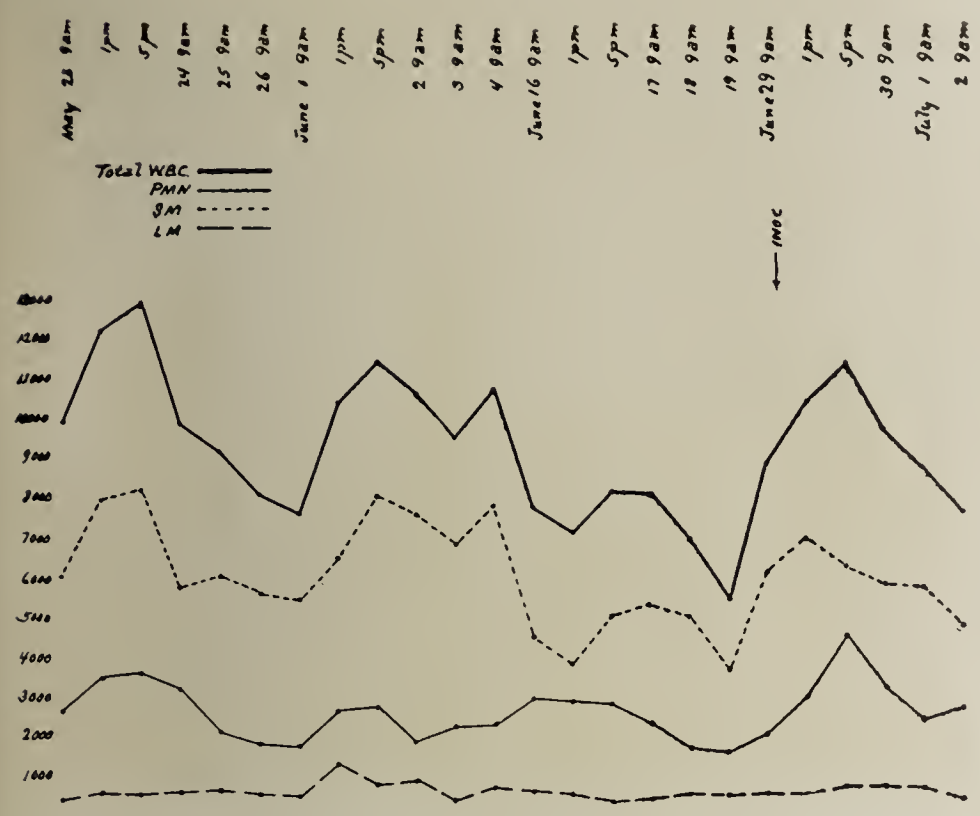

CHART XVII.

Rabbit No. 105 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

CHART XIX.

Rabbit No. 107 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

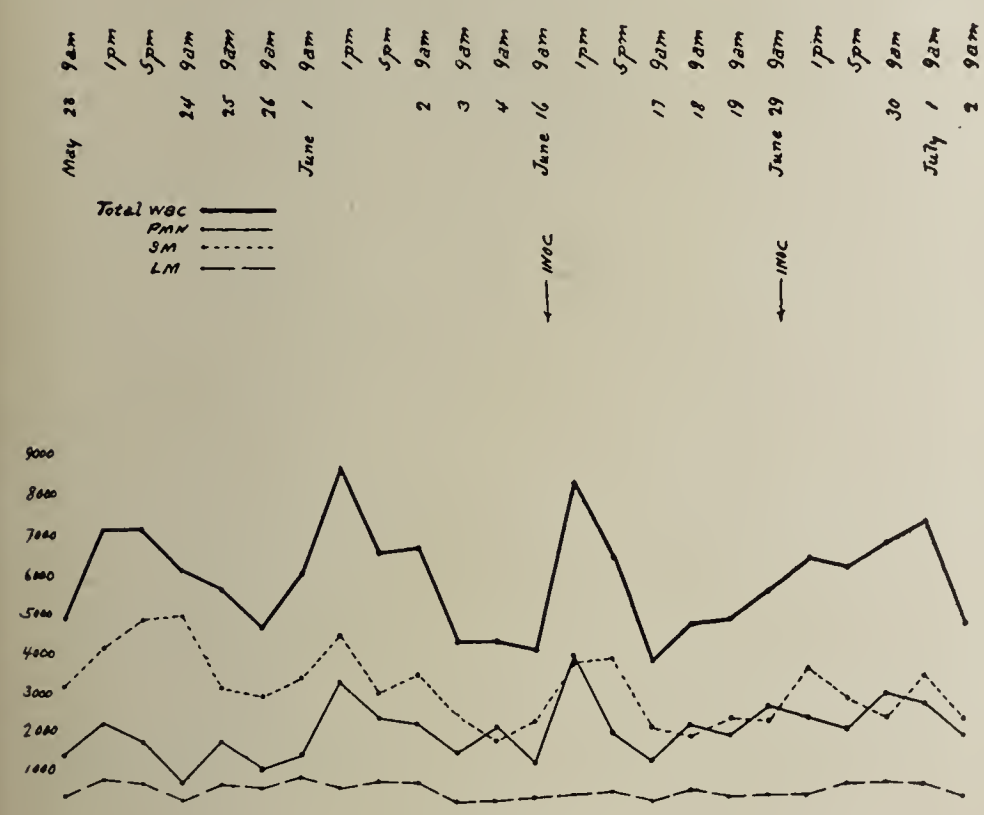

CHART XVIII.

Rabbit No. 106 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

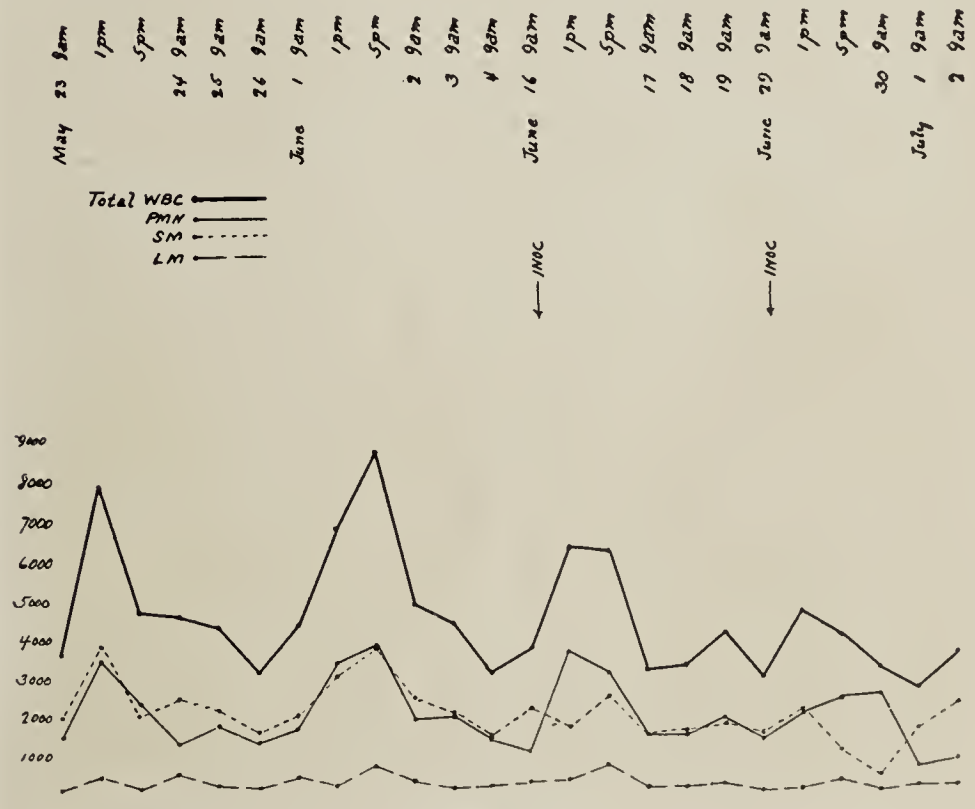

CHART XX.

Rabbit No. 108 showing total leucocyte counts and absolute values of polymorphonuclear, large and small mononuclear leucocytes for entire period of observation.

Rabbit No. 107—Cont.

		Total Leucocytes	Pmn %	Pmn Total	Lm %	Lm Total	Sm %	Sm Total	Eos %	Eos Total	Mst %	Mst Total
June	1, 9 a. m.	5180	43.5	2253	6.0	311	45.5	2357	1.5	78	3.5	181
	1 p. m.	5940	38.5	2287	10.5	624	49.0	2910	..	..	2.0	119
	5 p. m.	6960	48.5	3375	5.5	383	37.5	2610	0.5	35	8.0	557
	2, 9 a. m.	4040	35.5	1434	4.5	182	50.5	2040	1.0	40	8.5	343
	3, 9 a. m.	5260	16.0	842	8.0	421	70.0	3682	0.5	26	5.5	289
	4, 9 a. m.	5000	41.0	2050	4.5	225	49.0	2450	..	..	5.5	275
June	16, 9 a. m.	5200	33.0	1716	5.0	260	55.5	2886	0.5	26	6.0	312
	(Inoc. 2.5 cc. serum intravenously.)											
	1 p. m.	7140	30.0	2142	4.0	286	62.5	4462	0.5	36	3.0	214
	5 p. m.	6860	37.0	2538	6.5	446	46.0	3156	..	..	10.5	720
	17, 9 a. m.	5020	34.0	1707	7.0	351	53.0	2661	..	..	6.0	301
	18, 9 a. m.	3420	37.5	1283	7.0	239	51.5	1761	..	..	4.0	137
	19, 9 a. m.	3860	45.5	1756	11.0	425	34.0	1312	..	..	9.5	367
June	29, 9 a. m.	4300	35.0	1505	7.5	323	51.0	2193	..	..	6.5	279
	(Inoc. 0.01 cc. serum intradermally.)											
	1 p. m.	1800	..	..	..	..	..	..	..	..	..	..
	5 p. m.	6780	49.0	3322	6.0	407	39.0	2644	..	..	6.0	407
	30, 9 a. m.	8070	35.0	2824	8.0	646	52.0	4196	0.5	40	4.5	363
July	1, 9 a. m.	4960	52.0	2579	5.0	248	40.0	1984	..	..	3.0	149
	2, 9 a. m.	4140	35.5	4170	7.0	290	53.0	2194	1.0	41	3.5	145
Rabbit No. 108												
May	23, 9 a. m.	3600	40.0	1440	4.0	144	54.0	1944	1.0	36	1.0	36
	1 p. m.	7920	43.5	3445	5.5	436	48.0	3801	0.5	40	2.5	198
	5 p. m.	4700	51.5	2420	4.0	188	43.0	2021	..	..	1.5	71
	24, 9 a. m.	4540	28.5	1294	12.5	567	54.5	2484	..	..	4.5	204
	25, 9 a. m.	4280	40.5	1733	6.0	257	51.5	2204	0.5	21	1.5	64
	26, 9 a. m.	3160	41.0	1296	6.0	190	48.5	1532	2.0	63	2.5	79
June	1, 9 a. m.	4420	39.2	1654	10.8	456	46.8	1975	0.8	33	2.4	101
	1 p. m.	6840	49.5	3386	4.0	273	44.5	3044	1.0	68	1.0	68
	5 p. m.	8700	44.5	3871	8.5	739	43.5	3784	1.5	131	2.0	174
	2, 9 a. m.	4920	39.0	1919	8.5	418	50.5	2484	0.5	25	1.5	74
	3, 9 a. m.	4380	44.5	1949	4.0	175	47.0	2059	..	..	4.5	197
	4, 9 a. m.	3120	43.0	1341	8.0	250	46.0	1435	..	..	3.0	94
June	16, 9 a. m.	3740	30.0	1122	8.5	318	59.0	2206	0.5	19	2.0	75
	(Inoc. 5.0 cc. serum intravenously.)											
	1 p. m.	6340	58.0	3677	6.5	412	26.5	1680	0.5	32	8.5	539
	5 p. m.	6260	49.5	3099	12.0	751	36.0	2254	..	..	2.5	156
	17, 9 a. m.	3140	45.5	1429	6.5	204	45.5	1429	0.5	16	2.0	62
	18, 9 a. m.	3320	43.5	1444	5.5	183	47.5	1577	..	..	3.5	116
	19, 9 a. m.	4080	46.5	1897	6.5	265	43.0	1754	1.0	41	3.0	122
June	29, 9 a. m.	3020	45.0	1359	2.5	75	50.0	1510	0.5	15	2.0	60
	(Inoc. 0.01 cc. serum intradermally.)											
	1 p. m.	4660	43.0	2004	4.5	210	46.5	2167	3.5	163	2.5	116
	5 p. m.	4040	60.5	2444	10.0	404	27.5	1111	0.5	20	1.5	60
	30, 9 a. m.	3260	78.0	2543	3.0	98	13.5	440	0.5	16	5.0	163
July	1, 9 a. m.	2760	25.5	704	9.5	262	61.0	1683	0.5	14	3.5	96
	2, 9 a. m.	3620	25.5	923	6.5	235	64.0	2317	1.0	36	3.0	108

Chart XVI shows the total leucocyte counts for the entire series plotted out so that a general idea of the variations which have taken place can be gotten at a glance.

One sees that the leucocytes underwent as great changes in number during the two series of observations before inoculation as they did after inoculation. On May 23, June 1, 16 and 29, days on which counts were made at 9 a. m., 1 p. m. and 5 p. m., it is to be observed that the 1 p. m. count, or the 5 p. m. count, or both, are higher than the 9 a. m. count. This we ascribe to a digestive leucocytosis as in the preceding series, the animals being fed at 10 a. m. each day. We are unable to see that the intravenous injection of normal horse serum exerted any influence on the total number of leucocytes. It is possible that the depression of the digestive leucocytosis which is observable on June 29 may have been due to the intradermal inoculation.

Charts XVII, XVIII, XIX and XX show the total leucocytes and absolute values of the differential counts plotted out for rabbits Nos. 105, 106, 107 and 108, respectively. They illustrate very well the observation made in connection with the preceding series; namely, that both the polymorphonuclear and small mononuclear leucocytes participate in an increase in the total number of leucocytes, but in this series the small mononuclears, as a rule, participate to a greater extent than do the polymorphonuclears.* It is possible that the exception to this rule observable in Charts XVIII and XX, June 16, 1 p. m., where we see a relatively greater increase in the polymorphonuclear cells may have been due to the intravenous injection of normal horse serum, but inasmuch as similar exceptions are to be seen elsewhere in the charts where no horse serum was inoculated, it would hardly be safe to draw conclusions from these two instances.

Curves showing the total number of polymorphonuclear leucocytes for the entire series were superimposed for purpose of comparison and the same was done for the small mononuclears, but as the injection of serum seems to have been entirely without influence on either of these elements the charts are omitted.

* These results are in entire agreement with those obtained in a fourth series of counts which are not included in this report on account of lack of space.

Summary.

We have thought it worth while to publish these studies in full, giving the detailed counts for each series, since they represent a large number of carefully made observations and the data may be useful to others who are attempting to draw conclusions from variations of the leucocyte counts in rabbits.

We feel justified in saying that the normal variation in the total leucocyte count taken at the same hour each day of rabbits kept as nearly as possible under constant conditions is very great, at times reaching nearly 100 per cent.

We have observed quite regularly a diurnal cycle in which we are inclined to ascribe the increase in the number of leucocytes to the influence of digestion.

The relative and absolute values of the differential count vary under normal conditions from day to day and at different hours of the same day.

We observed that an increase in the total leucocyte count was participated in, as a rule, by both the polymorphonuclear and small mononuclear leucocytes, but usually by the latter to a greater extent than by the former.

The relative values (percentage values) of the polymorphonuclear and small mononuclear leucocytes bear a reciprocal relation to each other; that is, an increase in the percentage of one is accompanied by a decrease in the percentage of the other.

We were unable to observe that the intravenous injection of normal horse serum in doses varying from 0.1 cc. to 5 cc. or the intradermal injection of 0.01 cc. normal horse serum in either sensitized or non-sensitized rabbits had any definite or constant influence on the total or differential leucocyte counts, three hours or longer after injection.

We have a few observations, not included in this paper, where counts were made at short intervals (5-10 minutes) after the intravenous injection of large amounts (10 cc.) normal horse serum into rabbits. These indicate, as far as they go, that shortly after injection the total count undergoes a sharp decline with a marked relative increase of polymorphonuclear and decrease of small mononuclear leucocytes. These observations, however, were few in number and we hesitate to draw conclusions from them.

THE USE OF ANTIFORMIN IN THE EXAMINATION OF SPUTUM FOR THE TUBERCLE BACILLUS.

By W. W. BOARDMAN, M. D.

(From the Research Laboratory, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital.)

An absolute diagnosis of pulmonary tuberculosis can be based upon one, and only one finding—the demonstration of tubercle bacilli in the sputum. Yet in a review of the reports of various tuberculosis dispensaries and sanatoria we find that in the cases clinically diagnosed as definite pulmonary tuberculosis, the sputum is negative for tubercle bacilli in from 8 to 46 per cent. Are we to conclude then, that in from 8 to 46 per cent of our clinically positive cases, there are no tubercle bacilli in the sputum, and that these cases therefore are negligible factors in the spread of the disease; or that in a large proportion of these cases we fail to demonstrate tubercle bacilli, not because of their absence, but as a result of our imperfect methods of sputum examination, or our too careless use of these methods?

As to the first possibility; clinically positive cases without tubercle bacilli in the sputum do exist among the arrested cases and possibly in the very early stages of the disease, but there is no doubt that the number of cases so classed at the present time is too large.

The second possibility seems a more probable explanation. We fail to find tubercle bacilli in the sputum of many clinically positive cases, since (a) the specimen examined may contain no tubercle bacilli, being merely mucus from the upper air passages; or (b) if the tubercle bacilli are present in but small numbers, they may be overlooked, even in the most careful examination by the ordinary methods. This point is well illustrated by the following report by Goerres. In examining four smears from each of 296 specimens—96 were demonstrated to contain tubercle bacilli by the first smear, 24 more by the second, 9 more by the third, and 5 more by the fourth, and yet of the remaining 162 apparently negative sputa, 28 were demonstrated to contain tubercle bacilli by the antiformin method. Finally (c) as to the careless use of our present methods, it is evident, that if some cases escape detection even with repeated smear examinations, many may escape detection when but a single smear is made.

What then is the solution of the problem? It is evident that we must first obtain a specimen from the tuberculous lesion; again we must examine several smears from the same specimen; and lastly we must examine repeated specimens. The observance of these rules calls for the expenditure of much time and energy, and in return, although the results are fairly accurate, they still are far from perfect.

A more nearly absolute method, first proposed by Biedert[1] and slightly modified by subsequent investigators (Goerres[2]) has long been recognized as a valuable procedure, but the tedious technique has prevented its use except in a comparatively few doubtful cases. Briefly, the method is as follows:

A large quantity of sputum is well diluted with distilled water and 0.2 per cent sodium hydroxide is added, the material heated, stirring meanwhile, until a homogeneous solution results. It is then neutralized with acetic acid, and double the amount of 96 per cent alcohol added. It is then allowed to settle, the supernatant fluid is poured off and the sediment examined in the usual way. This method facilitates the finding of the bacilli by concentrating them in the sediment.

Following Biedert's first publication various agents were recommended for dissolving the mucus, such as hydrogen peroxide, carbolic acid, and pancreatic ferment, but none of these give so satisfactory results as the weak solution of sodium hydroxide with heat.

Thus matters stood until in the latter part of 1908, when Uhlenhuth[3] reported the results of his extensive researches with antiformin, a preparation much used by brewers in the disinfection of their fermentation vats and pipes.

Antiformin is a clear yellowish liquid of high specific gravity, possessing a faint chlorine odor and a decided soapy feel. According to Uhlenhuth it is composed of sodium hydroxide 7.5 per cent with sodium hypochlorite in such amount that 100 grams of antiformin liberates five and three-tenths grams of chlorine gas. After months of standing in the laboratory there is no appreciable deterioration.

As a result of his researches Uhlenhuth recommends antiformin as a disinfectant of the first rank, surpassing in many respects carbolic acid and bichloride of mercury. Its efficiency depends upon an intensive oxidation process, this being so marked that practically all organic matter except hair, wax, fat and cellulose, is rapidly brought into solution—the rate and completeness depending upon the strength of the solution used and the temperature at which the reaction occurs.

Upon adding a solution of antiformin to sputum, there is a marked liberation of gas. The sputum rises to the top of the mixture and rapidly dissolves, the result being a practically homogeneous solution, varying in color from yellowish-brown to a pale yellow, with but a small amount of flocculent sediment. The consistency of the resulting liquid varies directly with the consistency of the original specimen. The sediment varies in color from white to a dirty gray and consists of a finely granular detritus, fat needles, dust particles, cellulose fiber and any acid-fast organisms which may have been present in the original specimen.

A similar reaction occurs upon adding antiformin to finely divided animal tissues, pus, feces, suspensions of bacteria, etc. Uhlenhuth concludes that with the exception of one group of bacteria, all bacteria, protozoa, spirochætæ, and trypanosoma are dissolved in 2 to 5 per cent antiformin solution in from two and one-half to five minutes, the majority of them undergoing almost instantaneous solution. The organisms of the acid-fast group are the only ones resisting the dissolving

action of the antiformin solutions and this is explained by the fact that they are enveloped in a waxy capsule. Further work by Uhlenhuth and others revealed the important fact that tubercle bacilli, as shown by animal experimentation, are rapidly killed by antiformin only in 50 per cent or stronger solutions; that they retain their virulence for 12 days in 8 per cent solutions and for 4 days in 20 per cent solutions; finally that their staining properties are practically unaffected by exposure to 50 per cent antiformin for weeks.

We therefore have in antiformin an agent capable of rapidly and completely reducing sputum to a practically homogeneous solution without altering the staining qualities or viability of the contained tubercle bacilli. Several methods have been proposed for the recovery of the bacilli from these solutions, thereby making the procedure of practical value.

Uhlenhuth recommends simple sedimentation, his method for sputum examination being briefly as follows:

1. 15-30 cc. of sputum in a conical settling glass.
2. Add from three to five times the volume of water.
3. Add sufficient antiformin to make a 15 per cent solution.
4. Stir thoroughly and allow to digest and settle completely.
5. Pour off supernatant fluid.
6. Wash sediment with sterile water and allow sediment to reaccumulate.
7. Pour off supernatant fluid; smear sediment on slide and examine in usual manner.

The washing was found necessary since the presence of any considerable quantity of antiformin prevented firm fixing of the sediment to the slide.

Hüne [4] uses both the gravity sedimentation and the centrifuge. He proposes two distinct methods, as follows: *

I.

1. To a large quantity of sputum add antiformin to a 25 per cent solution.
2. After the production of a homogeneous solution add 96 per cent alcohol, thereby reducing the specific gravity and hastening sedimentation.
3. Pour off supernatant fluid.
4. Wash sediment in centrifuge.
5. Smear and examine.

II.

1. Take equal parts of sputum and sterile water.
2. Add antiformin to 2 per cent solution.
3. Allow to digest and sediment to accumulate.
4. Pour off supernatant fluid and smear directly.

In II washing is not necessary owing to the low percentage of antiformin; on the other hand, this process requires about three days for completion.

Meyer [5] also proposes two methods practically identical with the preceding:

* Hüne substituted a mixture of sodium hypochloride 11.1% and potassium hydroxide 5.6% for antiformin with satisfactory results.

I.

1. To the sputum add antiformin to a 20 per cent solution.
2. Transfer the entire resulting solution to centrifuge tubes and centrifugalize violently.
3. Wash sediment twice in centrifuge.
4. Smear and examine.

II.

1. To the sputum add antiformin to 3 per cent solution—examine sediment without washing.

Seeman [6] uses either the centrifuge method or gravity sedimentation. He also does away with the necessity of washing the sediment by using either diluted egg albumin or better, some of the original sputum to aid in fixing the smear.

METHOD.

1. To the sputum add antiformin to a 15-20 per cent solution.
2. Add 96 per cent alcohol after digestion is complete.
3. Smear sediment directly, using either egg albumin or some of the original sputum; or

2. Centrifuge the material.
3. Smear as in 3.

In using some of the original sputum to aid in fixing the smear, Seeman not only does away with the necessity of washing the sediment, but at the same time gains some insight into the general composition of the sputum, as regards the number and character of the other organisms, the type of cell predominating, and the presence or absence of elastic fibers; and also renders the search for the tubercle bacillus much easier by having the blue field upon which to focus.

Thilenius [7] uses the centrifuge after first having added alcohol to the sputum-antiformin mixture. He also uses antiformin in from 10-50 per cent solution.

Haserodt [8] recommends the use of ligroin, a light hydrocarbon oil, for obtaining the tubercle bacilli. His method is as follows:

1. To the sputum add antiformin to make 5 per cent solution.
2. Add a few cubic centimeters of ligroin and shake till an emulsion is produced.
3. Allow to stand until a sharp line of separation occurs between the ligroin and the sputum-antiformin mixture.
4. With platinum needle remove several loopsful of material from just below the ligroin; spread this on a slide and examine in the usual manner.

The tubercle bacilli and other undissolved particles in the mixture are carried upward by the little droplets of ligroin and deposited just below the line of separation between these two solutions. Haserodt claims that the smears, by this method, show no tendency to wash off the slides, but this statement is not upheld by other investigators. The method has no advantage over the previous ones, and has failed to give as good results.

Bernhardt's [9] procedure is exactly the same as Haserodt's, except he uses 5 cc. of sputum and adds 20 cc. of a 20 per cent solution of antiformin.

Goerres (*loc. cit.*), after carefully reviewing the work of other investigators, finally adopted the following method:

1. Equal parts of sputum and water.
2. Add antiformin to a 25 per cent solution, shake violently.
3. After 4-6 hours gently turn vessel to dislodge any particles which may be adhering to the side of the vessel.
4. Allow to settle for several hours.
5. Pour off supernatant fluid.
6. Fix sediment to slide with egg albumin or some of the original sputum.

The conclusions, finally reached from a review of the several articles dealing with the use of antiformin in sputum examinations, may be briefly summarized as follows:

1. Large quantities of sputum should be used.
2. Sputum should be diluted with sterile water.
3. Antiformin should be used in from 15-25 per cent solutions.
4. The sputum is dissolved in from 10-45 minutes—the bacilli, however, are uninjured after days of exposure in these solutions.
5. The resulting solutions should be watery in consistency and either colorless or pale yellow—if need be, more water or more antiformin may be added.
6. The tubercle bacilli may be obtained from the solution either by gravity sedimentation, by centrifugalization, or by the use of ligroin. Sedimentation may be facilitated by the addition of alcohol to lower the specific gravity. Of these several methods, gravity sedimentation is perhaps most used.
7. Washing of the sediment is unnecessary if egg albumin, diluted with 10 parts of water, plus 1 per cent formaldehyde; or some of the original sputum be used to fix the smear.
8. The smear stains perfectly by the Ziehl-Neelsen method.
9. In examining the smears one may find acid-fast rods which are to be differentiated from the tubercle bacillus by being larger, and straighter, and especially by the fact that they readily transmit light. These rods are probably fat needles, as suggested by Goerres.
10. In the entire smear there may be only two or three bacilli—but these are sufficient for a positive diagnosis.
11. Finally, by the use of antiformin in the examinations of sputum for tubercle bacilli one is enabled to demonstrate them in from 7.3 to 17.2 per cent of the specimens reported as negative after careful smear examination by the old method. This may be seen in the following reports:

Meyer (*loc. cit.*) in examining 113 sputa, found 14 positive by the ordinary smear examination. Of the remaining 99 so-called negative specimens, 14 or 14.1 per cent were demonstrated to contain tubercle bacilli by the antiformin method.

Haserodt (*loc. cit.*), in 340 examinations, classed 300 as negative after careful examination by the ordinary method. By the antiformin method 22 or 7.3 per cent of these negative sputa were shown to contain tubercle bacilli.

Goerres (*loc. cit.*), in 296 examinations by the ordinary method, found 162 negative; 28 or 17.2 per cent of these were definitely positive by the antiformin method.

Hüne (*loc. cit.*) reports 4 cases, repeatedly negative by the old method, proved positive by the new method.

Some months ago the writer undertook a study of the antiformin method of sputum examination to determine its value and limitations.

After trying various procedures, the following was finally adopted as the most satisfactory both as regards method and results.

1. Place the entire 24 hours' sputum in a conical settling glass; if the amount be excessive it is perhaps better to use only 15-20 cc.
2. If the specimen is thick, add an equal volume of distilled water. Less tenacious specimens do not require so much dilution.*
3. Add an amount of antiformin equal to one-fourth the volume of the diluted sputum; in other words, sufficient to make a 20 per cent solution.
4. Stir thoroughly, thereby breaking up the masses of mucus and greatly hastening complete solution.
5. Allow to stand till solution appears homogeneous. It should now be watery in consistency and pale yellow in color; if necessary, more water or more antiformin should be added and digestion allowed to continue. This will usually require from a few minutes to an hour, but may be allowed to continue for days with no resulting harm to the tubercle bacilli.
6. Add an equal volume of 95 per cent alcohol. By this procedure the specific gravity is reduced from about 1.030 to below 1.000; thereby not only hastening sedimentation, but making it more complete.
7. After stirring, allow to stand till sedimentation is complete. This will occur in 2-4 hours, but a period of 12-24 hours is recommended. During this sedimentation it may be necessary to gently turn the vessel to dislodge little particles of sediment which may be adhering to the sides of the vessel.
8. Pour off this clear supernatant fluid.
9. Make smear from the sediment on a glass slide, using some of the original sputum to aid in fixing the smear. This is best done by making a smear from the sputum before antiformin is added and afterwards spreading the sediment from the sputum-antiformin mixture on the same slide. Stain and examine in the usual way.

If one has the proper laboratory facilities the centrifuge may be used to hasten the work, or to remove the last trace of doubt as to the accuracy of the results; but from the reports of the other observers and my own exeprience, if tubercle bacilli are present, they will appear in the sediment obtained after adding alcohol. The use of the centrifuge merely shortens the time element, but in so doing adds much to the difficulties of the method.

Antiformin has been used in the examination of 103 sputa. Twenty specimens were obtained from the patients at Eudowood Sanitarium through the courtesy of Dr. Sloan, three from the Epstein Hospital, through the courtesy of Dr. Grover, and the remaining from the patients in attendance at the Phipps Dispensary of the Johns Hopkins Hospital. For the

* Here it might be well to make sure that the distilled water harbors no acid-fast organisms.

collection of the sputum wide-mouthed bottles of 100 cc. capacity were used, these being carefully washed in distilled water before being distributed. The patients were instructed to expectorate directly into the bottles, beginning with the first morning expectoration and continuing to use the bottles for the next 24 hours, or until they had accumulated from 15-20 cc. of sputum. However be it here noted that in this regard the results were very disappointing, as the dispensary patients frequently returned the bottles with but two or three cubic centimeters of sputum and in many cases this was without doubt entirely from the upper air passages. The results from the sanitaria were more satisfactory.

Dividing the cases examined according to the clinical diagnosis, 73 were definite pulmonary tuberculosis, 6 were probable pulmonary tuberculosis, 16 were doubtful pulmonary tuberculosis and 8 were definitely non-tuberculous.

By the old method all the sputa of the non-tuberculous, doubtful and probable groups, 30 in number, were negative. Of the 73 clinically positive cases, 31 showed tubercle bacilli in the smears examined.

By the antiformin method the examination of the same specimens showed no tubercle bacilli in any of the non-tuberculous, doubtful or probable cases. In the 31 cases positive by the old method great enriching was seen. In the ordinary smear an average of 25 bacilli could be counted in two minutes. In the antiformin smear an average of 138 tubercle bacilli could be counted in the same space of time. Of the 42 remaining specimens from clinically positive cases which, by ordinary smear examination, were negative for the tubercle bacillus, seven or 16.6 per cent were demonstrated to contain the bacillus by the antiformin method; or considering all the positive, probable and doubtful cases, a total of 95; 64 were negative by the old method, but 10.9 per cent of these were demonstrated to contain tubercle bacilli by the antiformin method.

I therefore feel fully justified in heartily recommending the use of antiformin in the examination of sputum for tubercle bacilli, not only in hospitals and dispensaries, but in the laboratory of every private physician. The general adoption of this method, combined with repeated examinations, will do much towards reducing the percentage of cases clinically diagnosed as definite pulmonary tuberculosis, in which however an *absolute* diagnosis cannot be made. Of far greater value than the finding of tubercle bacilli in the sputum of cases clinically diagnosed as definite pulmonary tuberculosis, is the possibility which this method offers of demonstrating bacilli in the cases still classed as only probable or doubtful, thereby enabling us to enforce a vigorous and systematic treatment at a time when such treatment is of most avail.

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SERUM TREATMENT OF HEMORRHAGIC DISEASES.

By W. L. Moss, M. D.,
Associate in Medicine, Johns Hopkins University,
AND
J. Gelien, M. D.
(*From the Research Laboratory, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital.*)

Under the designation "Hemorrhagic Diseases" is grouped a number of widely different morbid conditions, having hemorrhage as a common feature. The bleeding varies in location and in severity from insignificant cutaneous hemorrhages in mild cases of purpura, to appalling and even fatal losses of blood in more serious conditions.

An enumeration of the diseases with which hemorrhage is, or may be associated and which are sometimes designated as hemorrhagic diseases includes:

Hemophilia, hereditary and spontaneous.

Hemorrhagic diseases of the new-born, of which there are doubtless several forms.

Purpuras, acute, chronic, simple, rheumatic, senile, etc.

Jaundice.

Grave anemias.

A heterogeneous group, including nephritis, typhoid, and other severe infections.

Is hemorrhage in these conditions dependent upon a common cause or are different factors operative? At present we are unable satisfactorily to classify hemorrhagic diseases as we do not know the causes of the hemorrhagic diathesis, and in order to study this subject intelligently, a consideration of the theories of the coagulation of normal blood is necessary. There are almost as many theories concerning coagulation as there are investigators in this field. If we content ourselves with stating the points upon which all are agreed our task is easy. The coagulation of the blood depends upon the action of fibrin ferment, which normally is formed only after the blood is shed, on fibrinogen, which exists as such in the circulating blood. This much is fairly simple. Fibrinogen is a

protein body which forms 0.22-0.4 per cent of the plasma from which it can be obtained in approximately pure state, and its characteristics are fairly well determined. The part it plays in coagulation is known, but since hemorrhage is a pathological condition and coagulation does not take place under normal conditions, this action of fibrinogen can scarcely be taken as representing a normal function. Concerning its origin, the use to which it is put under normal conditions, and its fate in the body, we know little with certainty. The origin and mode of action of fibrin ferment is enveloped in still greater obscurity, although something is known of the finished product itself.

The term fibrin ferment is now used less than formerly, as the ferment nature of this body has been seriously called into question. Thrombin, as it was designated by A. Schmidt, has been isolated in approximately pure form and its properties studied by Howell.[1] Thrombin added to a solution of fibrinogen, causes coagulation by the formation of fibrin. Thus we have as factors in the much studied coagulation of the blood two substances, fibrinogen and thrombin which together form fibrin, the essential feature of the blood clot. Not only is the origin of thrombin the subject of many conflicting theories, but also the mode of action of thrombin on fibrinogen in the production of fibrin. Whether it is a ferment, a chemical, or a physico-chemical action is still undetermined.

Thrombin does not exist as such in the circulating blood, but since normally it appears within a few minutes after the blood is shed, it seems evident that all of the constituents which enter into its formation must be present in the blood before it is shed. Most theories concerning coagulation postulate, therefore, as a normal constituent of the blood, a mother substance of thrombin, usually designated prothrombin or thrombogen. While there can scarcely be a doubt as to the existence of prothrombin, it has never been identified or isolated. To account for the conversion of prothrombin into the active substance, thrombin, the presence of a ferment has been assumed, and to this ferment Morawitz gives the name thrombokinase. Since it has been found that blood does not coagulate if the calcium which it contains is precipitated in insoluble form as soon as the blood is shed, soluble calcium salts have been recognized as essential to the action of thrombokinase in converting prothrombin into thrombin. This kinase has never been isolated and its existence is really a matter of theory. Calcium salts of course do exist in the blood and their presence can be quantitatively determined, but the exact part they play in coagulation remains a subject of controversy.

Other substances which have been postulated in various theories to account for the coagulation of the blood, such as thrombozym, zymoplastic substances, etc., need not be considered here, but it is necessary, for the purpose of this paper, to go one step further into the theories concerning the formation of thrombin. We may accept as a necessary part of any theory, the existence of prothrombin normally in the circulating blood. Something happens when the blood is shed which causes the prothrombin to pass over into thrombin and since we have no more satisfactory explanation of this transformation we may refer it to the action of a kinase. But what is the source of kinase? There are numerous theories on this subject. There is one change in the blood which we know begins to take place as soon as it is shed, and this is the disintegration of the platelets, and less rapidly, the disintegration of the leucocytes. It is not unnatural, therefore, that investigators have sought the origin of thrombokinase in these elements.

We have attempted to develop from the literature, a more or less general and somewhat composite theory of coagulation. It serves to illustrate the highly speculative character of much that is held concerning this important phenomenon and indicates the difficulties to be overcome in arriving at the etiology and classification of the hemorrhagic diseases.

Hemophilia is the most striking and most interesting disease in this group and it is natural that it should have been most studied. To account for the hemorrhages many theories have been advanced. These vary from such simple explanations as abnormal thinness of the blood vessel walls, leading to rupture under slight provocation; abnormally high blood pressure; a disproportion between the total amount of blood and the total capacity of the vascular system; to such profound and obscure explanations as that "in hemophilia we have to do with an inherited chemical (fermentative) degeneration of the protoplasm of the formed elements of the blood, and perhaps of the whole organism" (Morawitz and Lossen[2]).

It is not necessary to enter into a discussion of the various explanations which have been offered for the hemorrhage in hemophilia and other hemorrhagic diseases. Some have thought that there is a lack of one or more of the factors normally present and concerned in bringing about coagulation; others have considered that there are present in the blood of these patients abnormal substances which are antagonistic to coagulation. Thus a lack of fibrinogen, of available calcium salts, of prothrombin, of thrombokinase, or of the elements from which thrombokinase is supposed to arise, on the one hand, and antithrombin and other anticoagulants on the other hand, have been held responsible for the failure of the blood to coagulate. Thus it may be seen that until more exact information is obtained as to the cause of the hemorrhagic diathesis any measure directed towards its treatment other than mechanical must be largely empirical.

When one comes to consider hemostatic measures one finds a long list for disposal. Excluding the direct measures, ligation, tamponading, etc., which are applicable to accessible hemorrhages in normal individuals, less successfully oftentimes in those with a hemorrhagic diathesis, we have the following: administration of calcium salts to increase the coagulability of the blood; injection of gelatin to increase its viscosity; administration of adrenalin to narrow the vessels. Unfortunately, the latter drug raises blood pressure, unless applied merely locally and while the local application does sometimes arrest hemorrhage, its use is accompanied by the danger, that if the hemorrhage does not cease entirely during the time the vessels are constricted, it is apt to become more profuse upon the subsequent dilatation, which occurs after the constricting action passes off.

Ergot probably has little value as a hemostatic aside from its use in obstetrics.

Other drugs which are classed as hemostatic are ferric chloride, silver nitrate, hydrastin, hydrastinine, gallic acid, lead acetate, etc. None of these, however, have proven very successful in the conditions under discussion.

Recently the treatment of hemorrhagic diseases has attracted renewed attention. It is to the investigations of Weil that the present trend of the work is usually ascribed. In 1905 he published his investigations concerning the pathogenesis and serotherapy of hemophilia,[3] which have been followed by numerous papers by himself and others.[4, 5, 6, 7, 8, 9]

Weil's work may be very briefly summarized as follows: The hereditary and spontaneous forms of hemophilia can be differentiated in origin, severity of clinical manifestations, character of the blood and its mode of coagulation. The faulty coagulation in the hereditary form is referred to the presence in the blood of anticoagulants; in the sporadic form, to the absence of substances normally present and essential to coagulation. He considers the changes of the blood in marked hemorrhagic conditions as analogous to, but not identical with, those of hemophilia and recommends, as a cure for the sporadic type of hemophilia and for many of the other hemorrhagic states and as the best therapeutic agent available in the treatment of hereditary hemophilia, subcutaneous injections of 30 cc. or intravenous injections of 15 cc. fresh human or animal serum. Eliçagaray [10] confirms Weil's work.

Baum [11] repeated much of Weil's experimental work, most of which he was unable to confirm. In reviewing his experience he states that he was much encouraged by his first case in which local applications of serum apparently stopped the hemorrhage, following the extraction of a tooth, in a hemophilic. In his succeeding cases, however, and in his animal experiments local applications of serum seemed entirely without effect. As to injections he found that in hirudinized rabbits, the coagulation time was much reduced by injections of serum, except in cases in which the blood had been rendered incoagulable to a marked degree by hirudin.

Baum treated three cases of hereditary hemophilia by means of serum injections with negative results, but thinks that in other hemorrhagic conditions good results may follow its administration.

Trembur [12] reports one case of hemophilia successfully treated by injections of sheep and rabbit serum.

Lommel[13] reports the successful treatment of hemorrhages in a four-year old hemophilic by the use of subcutaneous injections and local applications of antistreptococcic serum.

Class [14] reports one case of purpura hemorrhagica, which he considered cured by injections of antidiphtheritic serum.

Leary [15] reports a series of twenty cases treated by means of serum injections. His cases may be summarized as follows:

1. Jaundice, nine cases. The first case did not receive serum until after the hemorrhage had set in, following an operation. This patient died. Each of the remaining eight cases received before operation, as a prophylactic measure, 30 cc. rabbit serum subcutaneously. All but one of these recovered with but little bleeding following the operation. In the fatal case the author ascribes the death not to hemorrhage but to cholemia.

2. Hemorrhage of the new-born, three cases, two recoveries, one death.

3. Hemophilia, one case received diphtheria antitoxin, rabbit serum, and finally direct transfusion of human blood. Patient regained health rapidly.

4. Purpura, one case, cured.

5. Post operative hemorrhage, two cases, one cured, one died.

6. Uterine hemorrhage, one case, cured.

7. Typhoid fever hemorrhage, two cases, cured.

8. Ruptured tubal pregnancy (operated) one case, cured.

Among others who speak favorably of the use of serum injections in the treatment of hemorrhagic diseases is Welch,[16] who reports twelve cases of hemorrhage in the new-born, all of which he claims were cured by subcutaneous injections of fresh human serum. He injected as much as 209 cc. in five days, but averaged about 80 cc., in 10 cc. doses, extending over four days.

Schockaert [17] used subcutaneous injections of antistreptococcic serum successfully in two cases. One was a very anemic patient who bled profusely under operation. Fifty cubic centimeters of serum were injected and the author reports that immediately the hemorrhage stopped, so that the operation could be concluded with a dry field of operation. The second case was one of rebellious menorrhagia which resisted hydrastis, ergot, stipticine, etc., but was controlled by injections of 10 cc. of antistreptococcic serum at the beginning of the menstrual periods.

Chabrol [18] reports the successful serum treatment of a case of rheumatic purpura accompanied by intestinal hemorrhage which resisted ordinary treatment, calcium chloride, gelatin, ergot, etc. He gave daily injections of 10 cc. diptheria antitoxin subcutaneously for five days.

Bigelow [19] reports successful treatment of three cases of hemorrhagic disease of the new-born. He states that two of the cases were moribund when treatment was instituted, calcium lactate and epinephrin having been tried without benefit. The hemorrhages ceased after subcutaneous injections of 5 cc. fresh rabbit serum.

Busse [20] reports the use of fresh human serum in the treatment of 10 cases of uterine hemorrhage. The dose employed was 10 cc. injected intragluteally. Five of his cases he regarded cured, four were still under treatment at the time of his report.

A smaller number of reports have appeared in which the value of serum injections in hemorrhagic disease is denied. The authors of these reports usually advocate the use of injections of defibrinated blood instead of serum or else the direct transfusion of human blood. Thus Schwartz and Ottenberg [21] report the case of a child 11 days old with melena, hematemesis, hemorrhages from the nose and mouth, icterus and ecchymoses. One injection of horse serum (not fresh)

had no effect in stopping the bleeding. The child was therefore transfused from its father and the hemorrhages are reported to have immediately stopped. After some days, however, bleeding recurred and the patient died.

Mosenthal [22] reports a case of melena neonatorum cured by direct transfusion.

Swain, Jackson and Murphy [23] report a case of melena neonatorum unbenefited by 75 cc. of fresh rabbit serum subcutaneously and an injection of diphtheria antitoxin. Direct transfusion from the child's father was followed by complete cessation of the hemorrhage.

Lambert [24] reports a case of melena neonatorum in which transfusion was performed after the hemorrhage had been going on for three days and the child was in a dying condition. An immediate and permanent cure is said to have resulted.

Murphy [25] reports the case of a woman 48 years old, who for 17 years suffered attacks of abdominal pain, jaundice, clay colored stools and finally a very severe attack accompanied by hemorrhages from the nose and rectum. Injection of 30 cc. horse serum was without effect. Injection of 30 cc. fresh rabbit serum seemed to control the hemorrhages to a degree, but still the bleeding continued to an alarming extent. Coagulation time 13 minutes (Brodie-Russell). The patient was then transfused, her husband being the donor. Twelve hours after transfusion the coagulation time was 3-4 minutes and on the following day the patient was successfully operated on for gall stones, and was cured.

Duke [26] considers that the tendency to uncontrollable bleeding in at least some of the hemorrhagic diseases is due to a diminished number or to an absence of blood platelets. He therefore advocates transfusion as the only means of supplying the deficit and reports several cases which he considers to have been greatly benefitted by this procedure.

From this review of the literature, which is by no means complete, it is apparent that any treatment of these alarming and oftentimes dangerous conditions can be only empirical, until the cause of the disorder is determined. Meanwhile the use of serum injections, the injections of defibrinated blood, and direct transfusion seem to have yielded better results than any other measures. As to the choice between these three procedures, doubtless direct transfusion would be the ideal method were it not for the technical difficulties.

As to the intravenous introduction of defibrinated blood or foreign serum, one perhaps must feel some apprehension of danger, but the condition to be combated is a dangerous one and justifies, in the present state of our knowledge, the risk we may run in carrying out these procedures. Moreover, theoretically the danger from agglutination in transfusion is perhaps as great as the danger from thrombosis or hemolysis, following the injection of defibrinated blood or foreign serum. So far as we are aware no untoward results of a serious nature have been reported to follow the latter two measures. Finally, while it may be true that certain of the hemorrhagic diseases depend upon a lack of blood platelets and that this deficit can only be supplied by direct transfusion, still it is more probable that it is not the platelets *per se* which contribute towards the checking of hemorrhage, but products which are set free on their disintegration. These products are doubtless furnished just as well in serum or defibrinated blood as in the whole blood. It would seem that injections of serum or of defibrinated blood would answer as well as direct transfusion in all cases except those—if clinically there are such—which depend upon a lack of fibrinogen.

A consideration of great practical importance is, that in the case of injections of serum or of defibrinated blood one knows certainly that he gets the injection into the patient and one can accurately gauge the amount introduced, while in transfusion, except in the hands of an expert surgeon, there is much uncertainty of transferring any blood at all, and in no case can the amount transferred be satisfactorily determined.

Our series consists of six cases admitted to the wards of the Johns Hopkins Hospital.* The number is small and no conclusions should be drawn from them, but the results were so encouraging that the method seems to deserve further consideration.

In every case the serum or defibrinated blood was used within 2-3 hours after it was drawn, except in Case 4 where normal horse serum was used.

Case 1.—*Typhoid Fever.* Male, age 31, black, single, laborer. Admitted August 6, 1910.

Complaint: Headache and pain in back.

Family History: Not important.

Past History: Measles at 21; hard work as laborer; alcohol, weekly sprees.

Present Illness: Onset two weeks before admission,—headache and fever, also diarrhœa.

Physical Examination:. Well-nourished, muscular man. Tongue coated; general glandular enlargement; spleen palpable; sputum contained some blood clots. Hæmoglobin 100 per cent.

August 17: Bleeding from gums. Silver nitrate adrenalin chloride and calcium lactate without effect.

August 18: Ecchymoses appeared on conjunctiva and purpuric spots on abdomen. Hematuria. Red blood cells 2,912,000. Hæmoglobin 80 per cent.

August 19: Feces continue to contain blood; 13 cc. defibrinated human blood injected intravenously, followed by headache and restlessness.

August 20: 13 cc. defibrinated human blood, intravenously.

August 21: 17 cc. defibrinated human blood, intravenously.

August 22: 12 cc. defibrinated human blood, intravenously.

Following these injections the bleeding seemed less profuse but the blood count continued to fall and showed on the latter date, red blood cells 1,448,000. Hæmoglobin, 35 per cent.

August 23: In view of patient's desperate condition, 320 cc. of defibrinated human blood from a case of polycythemia was given intravenously. This was followed by headache, chill, extreme abdominal pain and rapid pulse.

August 24: Red blood cells 2,880,000. Hæmoglobin 40 per cent. Patient feeling much better but still slight oozing from gums and blood in his stools. 250 cc. defibrinated human blood was injected intravenously, followed by severe shaking chill with elevation of temperature and pulse.

August 26: 20 cc. defibrinated human blood intravenously.

August 27: 200 cc. defibrinated human blood intravenously.

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* We are indebted to Drs. Halsted, Barker and Thayer for permission to report these cases.

This injection was well borne, there being no chill or elevation of temperature after it. From this date convalescence was rapid, and no further hemorrhages occurred.

September 26: Red blood cells 3,344,000. Hæmoglobin 72 per cent. Patient discharged well.

In this case two serious conditions presented themselves, one resulting from the other; persistent hemorrhage and grave anemia. Large injections of defibrinated blood were used in this case rather than small injections of serum with the hope that the fibrin ferment introduced would check the hemorrhages and that the foreign red blood cells might continue their normal function in our patient and thereby relieve his anemia. The blood counts before and after the first large injection of defibrinated blood seem to indicate that this hope was realized.

It was considered by all those who observed this case that the injections of defibrinated blood exerted a favorable influence and were perhaps the means of preventing a fatal issue.

Case 2.—*Chronic Nephritis, Myocarditis, Uremia.* Male, white, aged 43, married, lumber merchant. Admitted October 13, 1910.

Complaint: Weakness, stupor and sour stomach.

Family History: Father dead, aged 73, heart trouble; mother, four brothers and one sister, living and well. Three sisters died of tuberculosis about 25 years ago. Married seven years, no children.

Past History: Whooping cough at 14, measles and gonorrhœa at 17. At 36 a diagnosis of tuberculosis was made; patient later was pronounced cured. Malaria at 41. Patient has used alcohol and tobacco until recently, two cigars and two or three drinks daily. Has done hard physical work with much exposure all his life.

Present Illness: Onset six months ago. Started with feeling of weakness, dullness and headache. Within twenty-four hours vomiting, delirium, convulsions. After two weeks patient was well enough to return to work, and kept about his business until one week before admission to the hospital. At this time (October 4) again had headache, vomiting and convulsions. Since the first admission, six months ago, patient states that he has been subject to headache, increased urination, dyspnœa, œdema of ankles and impairment of vision.

Physical Examination: Sparely nourished man, dull, urinous odor to breath, vision impaired. Systolic murmur at apex and over body of heart, transmitted to axilla. Well marked arteriosclerosis.

October 14: Red blood cells 3,100,000. White blood cells 16,800. Hæmoglobin 50 per cent.

October 15: Five hemorrhages from bowels; prior to this date stools contained no blood.

October 16: Five hemorrhages from bowels. Following the last hemorrhage 30 cc. of fresh rabbit serum was injected subcutaneously into the thighs. Following this injection, there was no further bleeding.

October 17: Red blood cells 1,700,000.

October 20: Patient sank into a deep coma and died.

Although this patient died, it is to be noted that there was an interval of four days between the injection of serum and death, during which no hemorrhage occurred.

Case 3.—*Cirrhosis of Liver (atrophic) and Hematemesis.* Male, white, aged 52, married, banker. Admitted October 19, 1910.

Complaint: Weakness, swelling of feet, and vomiting of blood in February, 1910.

Family History: Not important.

Past History: Measles as a child, typhoid at 37, recovery good. Very closely confined to business, takes little exercise; 6 to 10 cigars daily. Hearty eater. No alcohol. Constipation for past two years.

Present Illness: Eight months ago, when as well as usual, was taken suddenly with a feeling of weakness and vomiting of blood, passing considerable amount of blackish material from the rectum. Remained at home for one week and was in hospital for three weeks. Shortly after returning to business was constipated and had a fecal impaction removed by physician, after which for a time he enjoyed a feeling of perfect health. Several months prior to his present hospital admission he had an attack of indigestion accompanied by dizziness and vomiting at intervals of six or eight hours. Vomitus was at first blood stained.

Physical Examination: Large fleshy man, pale, skin slightly yellow, heart enlarged, loud systolic blow over precordium and in axilla. Red blood cells 1,846,000. White blood cells 5000. Hæmoglobin 39 per cent.

November 2: Patient suffered three attacks of hematemesis; was given morphine and calcium lactate.

November 3: Three attacks of hematemesis, vomiting approximately one liter of blood. Following the last hematemesis 30 cc. of fresh rabbit serum was injected subcutaneously.

November 4: Gradual onset of weakness, unconsciousness, and death.

There was no further evidence of hemorrhage after the administration of serum, but at autopsy the stomach was found to contain a large amount of dark blood.

Case 4.—*Chronic Pancreatitis, Jaundice, Exploratory Laparotomy, Drainage of Gall Bladder.* Male, white, aged 30, clerk. Admitted to hospital October 20, 1910.

Complaint: Sick stomach and jaundice.

Family History: Not important.

Past History: Generally healthy; measles in childhood.

Present Illness: Onset, according to patient, ten years ago. At this time he had pain in the right kidney region after any violent exercise and associated with this was severe pain in the right testis. Four years prior to admission had attack of severe abdominal pain, accompanied by nausea but no vomiting. These attacks recurred at intervals for two years; jaundice for the past year.

Physical Examination: Negative except for jaundice.

October 26. Exploratory operation for obstructive jaundice Chronic pancreatitis was found, the head of the pancreas obstructing the common duct. Drainage of gall bladder, no stones.

November 7: Eleven days after operation, patient began to bleed from the wound in the abdominal wall. Hemorrhage could not be controlled by the ordinary means. 20 cc. of normal horse serum (less than one month old) was injected intravenously, followed by chill and sharp elevation of temperature. There was no further hemorrhage, however, and patient subsequently made a satisfactory recovery from his operation.

This is perhaps the most striking case in the series. The extremely obstinate nature of the hemorrhages in jaundice cases is well known and so alarmed were the surgeons in charge of this patient that they were unwilling that he should wait the two or three hours necessary for obtaining perfectly fresh rabit serum.

The hemorrhage ceased after a single injection of normal horse serum and it seems justifiable perhaps to believe that the serum stood in a causative relation to this result.

Case 5.—*Typhoid Fever.* Male, white, aged 17, single. Admitted to the hospital November 12, 1910.

Complaint: Fever and pain in stomach.

Family History: Not important.

Past History: Always healthy. Seven months prior to admission operation for appendicitis.

Present Illness: Began six weeks before admission; headache, chills and anorexia.

Physical Examination: Sparely developed and undernourished, tongue coated. Spleen palpable and soft. Rose spots present. (Blood culture *B. typhosus.*) Red blood cells 4,900,000. White blood cells 6000. Hæmoglobin 75 per cent.

November 16: Red blood cells 4,600,000. White blood cells 3900. Hæmoglobin 63 per cent.

November 23. Intestinal hemorrhages aggregating approximately 1750 cc.

November 25: 15 cc. fresh rabbit serum intravenously. Since then there have been no further hemorrhages.

CASE 6.—*Typhoid Fever.* Male, white, aged 21, single. Admitted to hospital on October 4, 1910.

Complaint: Headache.

Family History: Not important.

Past History: Mumps with double orchitis, measles; otitis several times five years ago. Gonorrhœa one year ago. Tobacco and alcohol very rarely. Works in open air, exposed to weather.

Present Illness: Onset, with drowsiness ten days before admission; six days before admission pain in stomach, headache, soreness in legs, feverish, anorexia, cough and diarrhœa.

Physical Examination: Well nourished man, tongue coated, palpable spleen, rose spots. Red blood cells 6,148,000. White blood cells 5080. Hæmoglobin 98 per cent.

October 11: There were four intestinal hemorrhages, aggregating about 500 cc.

October 14: Hemorrhages continued and it is estimated that the total loss of blood amounts to approximately 2000 cc. On this date patient received 30 cc. of fresh rabbit serum, subcutaneously.

October 15—6 a. m.: About 75 cc. of blood was passed from rectum, but the patient's condition was much improved. 11 a. m, 30 cc. fresh rabbit serum injected subcutaneously. 8 p. m., about 100 cc. of dark blood was passed from rectum. Following this there was no further hemorrhage, but on October 19, patient showed signs of perforation and at operation an opening was found in the ileum through which fecal matter exuded.

October 23: Patient died of acute broncho-pneumonia.

In this case on the day following the first injection of serum there was approximately 175 cc. dark blood passed per rectum. It is possible that this was blood which had been shed into the intestine before the serum injection. The subsequent perforation (four days after) and death (eight days later) of the patient does not detract from the idea that the serum injections were successful in combating the hemorrhages.

The series of cases here reported is small and in several instances a fatal termination ensued, but it is to be remembered that the serum injections were not given in the hope of curing typhoid fever, nephritis, cirrhosis of the liver, etc., but to combat the hemorrhage which was associated with these conditions. If the hemorrhage was stopped by the use of serum injections, even though the patient eventually died, our hopes were fulfilled.

In our present state of knowledge, or lack of knowledge, concerning the causes of hemorrhages in these various conditions, the treatment is necessarily empirical. The most plausible explanation of any good which injections of serum or defibrinated blood may do is that fibrin ferment is thereby introduced into the circulation.

Since it is known that fibrin ferment (thrombin) readily passes over into an inactive form (meta-thrombin) on standing, it seems advisable to use serum or defibrinated blood as fresh as possible.

We have used rabit serum because it is easily obtained in a fresh condition, is but slightly, if at all, toxic for human beings, and if sensitization of the patient follows, the danger is not very great, since it is unlikely that subsequent administrations of rabbit serum would take place.

If horse serum is used one has to consider very carefully if the patient may not have been sensitized by a previous injection of antitoxin (horse serum) or may not be sensitized to a subsequent injection of antitoxin.

As to choice of methods, it seems advisable to inject directly into the circulation, although in so doing the possibility of causing intravascular clotting must be borne in mind.

If the patient has already been rendered anemic by serious hemorrhage, injection of large amounts of defibrinated blood directly into the circulation may not only check the hemorrhage but combat the anemia. With this end in view human blood should be used, since the red cells from one species cannot functionate in a different species, and it is likely that they would be quickly hemolyzed and give rise to toxic symptoms. In order to insure the best chance of success the donor should be a person from the same group (according to the isoagglutination reaction)[27] as that to which the patient belongs, thus avoiding possible danger from isoagglutination and isohemolysis.

In view of the unsatisfactory results attending the use of the ordinary methods of treating the hemorrhage in these conditions and the encouraging results from injections of serum and defibrinated blood reported here and elsewhere, we believe the later procedures are deserving of a more extensive trial.

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CONCERNING THE MUCH-HOLZMANN REACTION.

By W. L. Moss, M. D.,
Associate in Medicine, Johns Hopkins University,
AND
F. M. Barnes, Jr., M. D.,
Government Hospital for the Insane, Washington, D. C.
(*From the Research Laboratory, The Phipps Tuberculosis Dispensary, The Johns Hopkins Hospital.*)

Based upon the investigation of a considerable series of cases Much & Holzmann[1] proposed a biological test for the diagnosis of certain forms of insanity (dementia precox and maniacal depressive insanity) which they designate as the "psycho-reaction."

The reaction consists, according to the originators, in the ability of the serum from patients suffering from the two forms of insanity mentioned, to inhibit the hemolysis of normal red blood cells by cobra-venom; the serum from patients with other forms of insanity (epilepsy with circular disturbances excepted) and from normal individuals having no such action.

The authors carried out the test on the serum of 400 individuals and state that 100 per cent of all cases in which a diagnosis of dementia precox or maniacal depressive insanity could be established with certainty, gave a positive "psycho-reaction."

Much[2] reports the results of his investigation on additional cases, confirming his previous claims and considers the reaction dependent upon a quantitative or qualitative disturbance in the cholesterin content of the serum, due to altered metabolism indicating an inherited predisposition.

Bauer[3] objects to the term "psycho-reaction," as he does not consider the reaction a specific one.

He investigated the action of the serum from umbilical cord blood in 17 cases and found, that in the presence of 14 of these, no hemolysis of red corpuscles by cobra-venom took place, while in one case, only a trace of hemolysis occurred, and in the other two cases the hemolysis was partial.

In the presence of the serum of 16 older children and adults, the hemolysis was either partial or complete in every case; while in the presence of the serum of nine nursing infants no hemolysis occurred in one case, and was either partial or complete in the remaining eight.

Bauer thinks that the explantion of these results is to be sought in a paucity of activating lipoids in the serum (perhaps lecithin) rather, than in an increase of inhibiting substances (cholesterin).

Huebner and Selter,[4] using the same technic as Much and Holzmann, state the following results, which were the outcome of experiments with 82 cases of dementia precox, maniacal depressive insanity and other types of functional and organic psychoses and neuroses.

1. The cobra-venom reaction was found not only in cases of maniacal depressive insanity and dementia precox, but also in many other diseases, psychoses as well as neuroses and organic brain and spinal cord diseases.

2. The reaction was positive in less than 50 per cent of the positively diagnosed cases of maniacal depressive insanity and dementia precox.

Hirschl and Pötzl[5] found in a number of cases of the hebephrenic and catatonic forms of dementia precox, an increased resistance of the erythrocytes and an increased inhibiting action of the serum against cobra-venom hemolysis. They reserve their opinion as to the clinical value of the test.

Beyer and Wittneben[6] examined the blood of 345 individuals with reference to the Much-Holzmann reaction. Their results are given in the following table:

Positive reactions occurred in the following cases:

I.

Dementia precox	50%	=50%
Maniacal depressive insanity	31	
Epilepsy	60	
Idiocy	74	
Other psychoses	19	

II.

Somatic diseases	25%

III.

Normal	10%

from which they conclude that the reaction is of no differential diagnostic value. It appears to them rather as an expression of certain changes in metabolism, which can occur in the most different conditions, the exact mechanism of which, however, is unknown.

Fraenkel, Kathe and Bierotte[7] carried out the reaction in 92 cases, 58 of which were various types of psychoses, 26 were patients suffering from other than mental diseases. In 50 per cent of the psychoses a positive reaction was obtained, 23 per cent of the patients suffering from other diseases gave a positive reaction, while of eight normal individuals tested all gave a negative reaction; from which they conclude, that the reaction is not specific as claimed by the originators, but does differentiate between healthy and diseased individuals. They consider the reaction a quantitative rather than a qualitative one, since they found that all sera exert some inhibiting action. Differences in the resistance of the corpuscles of individuals were noted and in some cases, a given serum, when tested again one set of corpuscles, gave a positive reaction and when tested against other corpuscles gave a negative reaction.

No difference was found between active and inactivated serum. Controls were made to determine if the corpuscles were hemolyzed by the serum alone in any case (isohemolysis).

The authors consider that the Much-Holzmann reaction depends upon the relation between activating and inhibiting substances present in the serum. These bodies probably being lecithin and cholesterin.

Zalozieki[8] obtained the positive reaction, according to Much and Holzmann, in a number of different psychoses, as well as in normal individuals and almost constantly in the blood of the newborn. He considers the reaction diagnostically valueless and thinks that it depends upon the degree of muscular activity.

Schultz[9] tested the reaction in 151 cases and obtained a positive result in 50 per cent of all cases of dementia precox and maniacal depressive insanity. He also obtained positive results in a number of other psychoses and in some normal controls. A large number of his cases fell in the doubtful group, due to the difficulty of making a clear reading. Schultz could not find that various factors such as age, sex, temperature, pregnancy, general blood condition and state of nutrition were of any importance. The quantitative nature of the reaction is emphasized and he concludes that the reaction is of no diagnostic value. The relative amount of cholesterin and lecithin present, according to Schultz, will determine the outcome of the test.

Geissler[10] examined 500 cases and points out that it is necessary to select the time for testing the serum according to the clinical state of the patient, as the reaction is generally negative in the intervals between attacks of maniacal depressive insanity and is more often present in those phases of dementia precox associated with periods of definite excitement or depression. Using these precautions he obtained a positive reaction in all cases of dementia precox and maniacal depressive insanity, but found positive results in other types of psychoses, as well as in non-psychic diseases. Geissler did not confirm Much and Holzmann's claims as to the positive reactions in cases of epilepsy and in those having a family history of dementia precox and maniacal depressive insanity. Eisner and Kronfeld[11] found the reaction positive in 57.8 per cent of 19 cases of dementia precox and in 50 per cent of eight cases of maniacal depressive insanity. Although they found about the same percentage of positive reactions in other psychoses and a somewhat smaller percentage of positive reactions in mentally sound individuals, they conclude that the reaction occurs with greater frequency in the psychoses as a class, than in other states. As to the diagnostic value, they cannot confirm the work of Much and Holzmann.

Plaut[12] examined 21 cases in all and found a positive test in 38 per cent of the cases of maniacal depressive insanity, and in 20 per cent of the dementia precox group. He concludes that the reaction is of no diagnostic value as proposed.

Brueckner and Much,[13] after the study of 200 more cases, conclude that although the reaction is of great theoretical serologic interest, it is not of use in the diagnosis of dementia precox and maniacal depressive insanity as originally claimed. They point out that before the reaction can be of use in psychiatry it will be necessary to determine the nature of the inhibiting substances, the factors concerned in their appearance in the blood serum, and the apparent relation existing between their higher prevalence in mental diseases than in all others examined so far. They offer no solution.

Rosanoff,[14] after the examination of 185 persons, concluded that all human sera possess some power of inhibiting the hemolytic action of cobra-venom, but that the degree of inhibition is not sufficiently raised or uniform in cases of dementia precox or maniacal depressive insanity to make the test of diagnostic value. A positive reaction was obtained in other psychoses and in normal individuals. The fact that so high a percentage of those suffering with dementia precox (57.9 per cent) gave a positive reaction, led Rosanoff to believe that a positive test might add weight to the diagnosis in certain doubtful cases, where there were other symptomatological factors leading to the conception of dementia precox. All 15 cases of maniacal depressive insanity gave negative results in Rosanoff's hands.

Pfoeringer and Landsberger[15] conclude that the cobra-venom reaction is not specific in the sense of Much and Holzmann. They consider it the expression of general changes in metabolism, especially in oxidation processes, in which the

red blood corpuscles play the most important rôle; at any rate, they do not consider this idea so hypothetical as the views of those who connect the reaction with processes in the central nervous system, which have to do with changes in the lecithin and cholesterin content of the blood.

Alt,[16] without giving any of the details of the work upon which his conclusions were based, says, that in the 50 instances, in which the reaction was tried, he was unable to obtain results which would in any way permit of conclusions in agreement with those of Much and Holzmann.

Omorokow[17] found that the Much-Holzmann reaction occurred more commonly in the psychoses as a class than it did in the surgical cases and mentally normal individuals examined by him.

Nitsche, Shlimpert and Dunzelt[18] in 198 cases, of which 105 were dementia precox and 28 maniacal depressive insanity, found positive tests in 54.2 per cent of the former and 14.2 per cent of the latter. The duration of the disease, age, sex, drugs and nutritional state apparently exert no influence on the outcome of the reaction. Opposed to Geissler[10] they can find no interdependence between the results and the stage or clinical phase of the disease in question. The reaction is not considered as diagnostic of either dementia precox or maniacal depressive insanity.

Raubitschek and v. Dungern[19] in the discussion of the report by Much (*loc. cit.*) indicated that they could find no regularity in the results of the test as applied and that they found positive results in a great number of conditions other than dementia precox and maniacal depressive insanity.

Stilling[20] investigated 50 cases of dementia precox, repeating the work of Hirschl and Pötzl and found the resistance of the corpuscles to hemolysis by cobra-venom increased in only 14 cases. Twenty-two cases gave a positive Much-Holzmann reaction, when tested against corpuscles from cases of dementia precox.

The author is unable to confirm the results of either Hirschl and Pötzl or Much and Holzmann.

Bonfiglio[21] at the end of his examination of 67 cases states that the reaction of Much and Holzmann is not specific for either maniacal depressive insanity or for dementia precox. In other details, his experience has been that of almost all others, who have repeated the work. In a second communication[22] he gives a review of the literature which has appeared on this subject during the past several months.

From the foregoing summary of the literature it appears that no diagnostic significance can be attached to the Much-Holzmann reaction. Our own conclusions on this point are in accordance with those of the majority of investigators who have repeated Much and Holzmann's work. We have, however, made certain additional observations which we think justify the publication of our results.

The points which we have tried to determine may be briefly stated as follows:

1. Does the serum from cases of dementia precox and maniacal depressive insanity inhibit cobra-venom hemolysis?

2. Does a given serum always give the same reaction when subjected to the Much-Holzmann test?

3. Is the result of the test influenced by the relation between the groups (as determined by the isoagglutination reaction) to which the serum and corpuscles belong?

4. Is there any difference between the action of fresh and inactivated serum on cobra-venom hemolysis?

5. Do corpuscles of different groups offer different degrees of resistance to hemolysis by cobra-venom?

6. Does serum favor or retard the hemolysis of human erythrocytes by cobra-venom?

Technique.—In the first series of cases we followed exactly the technique given by Much and Holzmann. The cobra-venom was obtained for us from Drs. Flexner and Noguchi of the Rockefeller Institute of New York by Dr. H. J. Berkley. It consisted of a 1 per cent solution in 50 per cent glycerine. This stock solution was kept in the ice chest and from it fresh dilutions were made for each series of tests.

From the first experiments it was evident that this venom had much greater hemolytic strength than that used by Much and Holzmann, so that after a few preliminary tests it was found necessary to use a 1-25000 dilution instead of a 1-5000 dilution as recommended by the originators. Later we further modified the technique in that we combined equal parts (0.25 cc.) of cobra-venom solution, serum, and a 5 per cent suspension of washed corpuscles, instead of 0.35 cc. serum, 0.25 cc. cobra-venom solution and 0.5 cc. of a 10 per cent suspension of corpuscles. The modified technique gave better results in our hands than that proposed by Much and Holzmann.

Considerable difficulty was experienced in reading the results of the test, as we got all grades of hemolysis from very slight up to complete, no matter how we varied the proportions of serum, corpuscles, and venom (the differences were as great in tests with normal serum as in those with serum from cases of dementia precox or maniacal depressive insanity), so that in our series a considerable number of cases fall into the group giving doubtful reactions.

We made no effort to collect a large series of cases, but on the other hand repeated the test a number of times with serum from the same cases on different days, and frequently put up parallel series, using corpuscles from a different person in each series.

We have tested the serum of 49 individuals with the following results:

TABLE I.

Number of Cases	Condition	Positive reactions	Negative reactions	Doubtful reactions
21	Dementia precox	9	7	5
4	Maniacal depressive insanity.	2	2	0
8	General paresis	1	6	1
16	Sundry other psychoses.....	0	6	0
10	Diseases other than mental and normal	2	3	5

A number of the above cases were tested on two, three, four and five occasions, but without any reference to psychic states. The results for a few of these cases, chosen at random from a considerable number of cases in which repeated tests were

made, are given in Table II. They show that the reaction is fairly constant for a given individual, varying sometimes from doubtful to positive or from doubtful to negative, but only once, Case 6, from negative to positive.

TABLE II.

Case Number	Oct. 19th 1909	Oct. 27th 1909	Nov. 5th 1909	Nov. 8th 1909	Nov. 17th 1909	June 25th 1910
1	—	—	±	—	±	
2	—	—				
3	±	+	+	+	±	
4	±	±	±			
5	—				±	
6	—		+	+	±	
7	—				±	
8	+		+	+	+	
9	+	+				
10				+	+	+

In performing the "psycho-reaction" Much and Holzmann recommend that the serum be tested against several different sets of corpuscles rather than against a single set.

It has been shown [23] [24] that individuals may be divided into four groups according to the isoagglutinative action of the serum and corpuscles. Isohemolysins have long been known to exist normally in human serum and recently it has been shown [24] that the serum of every individual possesses an anti-hemolysin which will protect not only his own corpuscles from isohemolysis, but also those of any member of the group to which he belongs.

It occurred to us that perhaps human serum might have some such protective action as the above against cobra-venom hemolysis; that is, that a given serum might protect its own corpuscles and others belonging to the same group from hemolysis by cobra-venom, and that a positive Much-Holzmann reaction (inhibition of hemolysis) might occur when the serum tested came from a member of the same group as that to which the individual belonged whose corpuscles were used in the test, and that a negative reaction (hemolysis) might result, when the serum and corpuscles came from different groups.

We further thought that negative reactions might result in some cases from the well known isohemolytic action of certain sera.

In order to determine these two points we always determined the group to which the serum belonged and also tested to see if it possessed an isohemolysin for any of the corpuscles used, and in a considerable number of cases we set up parallel series of tubes so that each serum was tested against corpuscles from several different groups. A single series will serve to illustrate the results.

With regard to the groups to which the serum and corpuscles belonged, reference to Table III shows that, except for very minor variations in degree, the hemolysis proceeds equally well when the corpuscles and serum belong to the same group as when they are from different groups. Furthermore, corpuscles in the presence of their own serum are hemolyzed by cobra-venom to the same extent as in the presence of serum from another individual, provided the latter contains no isohemolysin for the corpuscles in question.

With regard to the effect of isohemolysis on the result of the Much-Holzmann reaction, we encountered but few sera in our series which were hemolytic for the corpuscles used, but as far as our observations go, they tend to show that if a given serum is tested against several sets of corpuscles and is found to be hemolytic for one set but not for the others, this serum may give a positive Much-Holzmann reaction when tested against the corpuscles for which it is not hemolytic and a negative reaction when tested against the corpuscles for which it is hemolytic.

TABLE III.

Showing the Relation Between the Groups to Which the Serum and Corpuscles Belong and Contrasting the Action of Active and Inactive Serum.

Venom	Serum. No.	Serum. Gr.	Corps. Gr.	2 hours at 37° C. Serum active	2 hours at 37° C. Serum inactive	22 hours in ice chest Serum active	22 hours in ice chest Serum inactive
0.25cc.	20	IV	II	gK	gK	L	L
"	"	"	III	gK	gK	L	L
"	"	"	IV	gK	K	L	fvL
"	21	II	II	fvH	gK	kK	kK
"	"	"	III	gK	gK	kK	kK
"	"	"	IV	fvH	gK	kK	kK
"	22	II	II	gK	gK	L	fvL
"	"	"	III	gK	gK	L	fvL
"	"	"	IV	gK	K	fvL	fvL
"	23	IV	II	gK	gK	kK	K
"	"	"	III	gK	gK	kK	K
"	"	"	IV	fvH	gK	kK	K
"	24	IV	II	K	K	L	L
"	"	"	III	K	K	L	L
"	"	"	IV	K	K	L	L
"	25	IV	II	fvH	gK	kK	kK
"	"	"	III	fvH	gK	kK	kK
"	"	"	IV	fvH	gK	kK	kK
"	26	II	II	gK	K	fvL	fvL
"	"	"	III	gK	gK	fvL	fvL
"	"	"	IV	fvH	K	fvL	fvL
"	27	II	II	fvH	gK	fvL	kK
"	"	"	III	fvH	gK	fvL	kK
"	"	"	IV	fvH	gK	fvL	kK
"	28	IV	II	K	gK	L	fvL
"	"	"	III	K	gK	L	fvL
"	"	"	IV	K	K	L	fvL
"	29	IV	II	K	K	L	L
"	"	"	III	K	K	L	L
"	"	"	IV	K	K	L	L
"	30	IV	II	gK	gK	fvL	kK
"	"	"	III	gK	gK	kK	kK
"	"	"	IV	gK	gK	kK	kK
"	31	IV	II	gK	gK	fvL	fvL
"	"	"	III	gK	gK	fvL	fvL
"	"	"	IV	gK	gK	fvL	fvL
"	32	II	II	gK	gK	fvL	fvL
"	"	"	III	gK	gK	L	fvL
"	"	"	IV	fvH	gK	fvL	fvL
"	33	III	II	fvH	fvH	kK	kK
"	"	"	III	H	fvH	kK	kK
"	"	"	IV	fvH	fvH	kK	kK
"	34	IV	II	gK	gK	fvL	fvL
"	"	"	III	gK	gK	fvL	fvL
"	"	"	IV	gK	K	fvL	fvL

The grade of hemolysis is estimated by the color of the supernatant fluid and the amount of sediment in the tube.

H = no hemolysis.
fvH = trace hemolysis.
gK = large sediment.
K = sediment.
kK = small sediment.
fvL = almost complete solution.
L = complete solution.

The corpuscles used in the above series were from cases Nos. 32, 33, 34.

In several series of experiments we contrasted the effect of active serum and serum inactivated at 56° C. for 30 minutes, on cobra-venom hemolysis. Table III gives one such series and shows that there was only a slight and inconstant difference between the two.

We could discover no difference in the resistance of corpuscles of different groups to hemolysis by cobra-venom and our experiments to determine if serum favored or retarded cobra-venom hemolysis gave inconstant results with different sera.

Summary.

1. We concur in the prevalent conclusion that the Much-Holzmann reaction has no diagnostic significance.

2. The influence which a given serum has on cobra-venom hemolysis is fairly constant.

3. The relation between the groups to which the serum and corpuscles belong has no influence on the result of the Much-Holzmann reaction provided the serum contains no isohemolysin for the corpuscles used.

4. There is practically no difference in the effect of active and inactivated serum on cobra-venom hemolysis.

5. Corpuscles from normal individuals belonging to different groups vary in their resistance to cobra-venom hemolysis to a very slight extent.

6. The action of different sera in favoring or retarding cobra-venom hemolysis is inconstant.

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A SYNOPSIS OF STUDIES ON PERITONEAL ADHESIONS WITH A CONTRIBUTION TO THE TREATMENT OF DENUDED BOWEL SURFACES.

By Edward H. Richardson, M. D.,

Instructor in Gynecology, Johns Hopkins University.

It is scarcely necessary nowadays in a consideration of post-operative peritoneal adhesions to include convincing data as to the reality, scope and importance of this surgical problem. All of us know how frequently troublesome adhesions occur as a mortifying post-operative complication, even in our best hospitals and at the hands of our most skilful surgeons. Impressed by several striking instances of this character which have come under my observation during the past few years, I was led recently to undertake a systematic study of the entire available literature upon this subject, in order, if possible, to arrive at some definite conclusions regarding the pathology, the etiology, the prevention and the treatment of peritoneal adhesions. In a later publication I hope to present a complete analytical study of this voluminous material, with detailed references to the original contributions upon which I have based the opinions about to be expressed. It is my purpose in this communication simply to present a brief synopsis of this work in connection with a description of a new method of treating denuded bowel surfaces.

At the outset it is well to recall certain familiar characteristics of the peritoneum itself which have an important bearing upon this subject.

We are apt to forget the enormous area of this serous membrane, which has been estimated to be only slightly less than that of the skin.

Again, its remarkable absorptive power is sufficiently striking to have actuated a large number of investigators to undertake elaborate and laborious researches to determine its mechanism. As a result of this work we now know that fluids and soluble substances are, for the most part, absorbed by the blood vessels, while solid particles—such as coloring matter in suspension, bacteria, oil globules, etc.—are taken up by the lymphatics. Furthermore, that the lymphatic absorption is most active in the upper part of the abdomen, especially on the under surface of the diaphragm, and in the omentum, while in the pelvis it is sluggish—a fact now commonly taken advantage of by surgeons in the use of the Fowler's, or sitting, posture in the treatment of peritoneal infections.

It seems definitely established too that the very sensitive epithelial covering of the peritoneum is continuous, and not perforated by numerous stomata, or direct channels of communication between the peritoneal cavity and the lymphatic vessels, as was until quite recently taught. Closely allied with its absorptive power is its well-known ability to successfully cope with an astonishing amount of infection without itself being seriously or permanently damaged.

Then, too, it is important to remember that different portions of the peritoneum vary very greatly in sensitiveness to pain; in a general way the visceral portion being insensitive, while perhaps no tissue in the body exhibits quite the same exquisite sensitiveness to pain as do the parietal layers of this serous membrane.

Finally, one of its most striking characteristics is the rapidity with which it can form adhesions—a piece of gauze introduced into the abdomen during the course of an operation becoming quite snugly fixed to the visceral surfaces within a period of twenty minutes—a fact that is daily taken practical advantage of by surgeons in the disposition of protective gauzes during operations upon infected areas, and which adds materially to the sense of security afforded by gauze pads alone. This characteristic is also very intimately involved in the whole question of peritoneal drainage, and constitutes further one of nature's admirable methods of protection against peritoneal insult, as exemplified in the walling-off of an appendix abscess.

Perhaps less striking, but to my mind even more remarkable, is the completeness with which the peritoneum may absorb adhesions, and indeed completely eradicate all traces that would indicate their previous existence. From the evidence in hand it would seem to be a perfectly safe assertion to make that adhesions invariably follow laparotomy, yet how common it is nowadays to find no traces of them at a later second laparotomy!

Now obviously, all of these fundamental and important characteristics of the peritoneum, which are familiar to everyone, must be reckoned with in studying the process of adhesion formation, and in any attempt to control or prevent it. Happily we now know, as a result of much careful experimental and clinical study, quite accurately the pathological changes involved. Categorically stated, they are, in order of sequence, injury or death of the endothelium, pouring out of coagulable exudate, agglutination, organization, fibrous tissue formation, and a final termination in a contracted scar. There is a very attractive theory, supported by creditable experimental work, that the permanence or subsequent resolution of adhesions depends upon the fate of the surface endothelium. If the cells are capable of recovering from insult sustained, the process of adhesion formation advances no farther than the stage of agglutination, and later entirely disappears; but if, on the other hand, the injury has been sufficient to effect the death of the endothelium, organization proceeds and the adhesions become permanent. It seems to me, however, that further experimental confirmation is needed before we can accept this view without modification.

In view of the pathology of peritoneal adhesions just outlined, it is not surprising to find the bulk of the literature on their etiology concerned with a study of the various agencies ordinarily coming in contact with the peritoneum that might be considered inimical to the vitality of its endothelium. For the sake of brevity and clearness we may classify these contributions according to subject-matter as follows: (1) Blood; (2) Sutures and Ligatures; (3) Eschar of the Thermo-cautery; (4) Air; (5) Infection; (6) Mechanical, Chemical, and other Agents.

Blood.—The final verdict has not yet been given regarding the relationship of free blood in the peritoneal cavity to adhesion formation. After carefully and impartially weighing the evidence before me, however, and in the light of my own observations, especially in cases of ectopic pregnancy, it is my deliberate judgment that blood alone does not cause peritoneal adhesions. Although frequently associated, the presence of adhesions can always, in my opinion, be more rationally explained in other ways than on the assumption of irritation from the blood.

Sutures and Ligatures.—Much of the older literature has to do with the question as to whether or not aseptic sutures and ligatures constitute an important factor in the production of adhesions. Mass ligatures and pedicle stumps, too, are accorded significant consideration. But while this whole subject of the ultimate fate of the various sutures and ligatures used in the tissues of the peritoneal cavity furnishes a study of absorbing interest, I shall have here to assume familiarity with it, and dismiss the matter with the statement that where one exercises good surgical judgment and manual dexterity in the choice and application of aseptic sutures and ligatures, no grave fears need be entertained as to troublesome adhesions arising from this source.

Eschar of the Thermo-cautery.—The results of the experimental work on the use of the thermo-cautery in the peritoneal cavity have been somewhat conflicting. The reason for this is probably to be found in a fact brought out by some of the later work, namely, that a superficial burning generally gives rise to adhesions, while a deep thorough cauterization with the formation of a thick eschar, does not produce adhesions. The explanation offered is that the charred surface protects the granulating surface beneath from exposure until it becomes covered with new endothelium. However true this may be, the weight of experimental and clinical evidence certainly warrants the thorough application of the cautery when indicated with far less likelihood of adhesions ensuing than if certain other procedures applicable to the same conditions are substituted.

Air.—Exposure of the viscera to the air is recognized, of course, as one of the cardinal factors in the production of surgical shock. It may not be so generally known, however, that much experimental work of the highest order has been done to ascertain the effect of the air on the peritoneal endothelium, and its relation to adhesion formation. Unfortunately, here again the results are conflicting; but the evidence is decidedly in support of the view that the air, even

when freed from dust and infection, does exert a deleterious effect on the endothelium. The most plausible explanation of its action is that rapid absorption of heat and moisture from the peritoneal surfaces occurs, and as a result of this drying and cooling process, a necrosis of the endothelial cells is produced, with resulting contraction of the blood vessels and diminished nutrition, all of which stand in etiological relationship to adhesion formation. Thus, aside from the prevention of shock, we have an additional very important reason for carefully protecting all parts of the peritoneum from undue exposure during the course of abdominal operations.

Infection.—No one doubts, of course, that infection produces adhesions. But there seems to be much difference of opinion as to the formation of adhesions without infection. A number of observers have called attention to the gradual falling off in the number of adhesion cases seen in the clinics corresponding with the improvement in surgical technique. Some have interpreted the remaining incidence, however, as conclusive evidence that our methods are still imperfect as regards asepsis.

The work of the experimental investigators, while admirable in its thoroughness, has unfortunately confused rather than simplified matters, by reason of the conflicting results obtained. No phase of this whole subject has evoked a sharper controversy than the question of infection in its relation to adhesion formation, and the alignment can be sharply drawn between the adherents of two views: (1) those who hold that infection is the sole cause of adhesions; (2) those who hold infection to be the chief cause, but admit that they do result from various other causes acting independently or collectively. The latter group are unquestionably right, as is conclusively proven, not only from a comprehensive study of the whole problem of adhesion formation, but indeed is tacitly admitted by their opponents through the conspicuous absence of any recent substantiation of their claims. No one, as far as I know, is contending nowadays that adhesions can only be produced by infection.

Mechanical, Chemical and other Agents.—Under this heading are to be included nearly all of the various fluids and chemicals formerly so extensively used and constituting the major part of antiseptic surgical technique. All this has been replaced, of course, by our modern aseptic methods, and the experimental as well as the clinical evidence testifies undeniably to a consequent diminution in the number of adhesion cases seen.

Abundant experimental proof is available to support the generally accepted view that raw surfaces, resulting from direct mechanical insult to the peritoneum, are one of the commonest, if not the most frequent, cause of adhesions. So, too, foreign bodies inadvertently left in the abdominal cavity, as well as the various types of drains purposely introduced, invariably provoke adhesions. In this connection too much emphasis cannot be given to the importance of exercising the utmost care and gentleness in all intraperitoneal manipulations. Rough handling of the viscera; unintelligent, and I might say sometimes almost brutal, use of retractors and other instruments; mauling the bowel surface by the introduction of innumerable gauze pads, which, to be sure, add materially to the comfort of the operator, but more to the distress of the patient; the application of dry gauzes to the peritoneal surfaces, which generally adhere, and when removed often bring away with them the surface endothelium; unnecessary sponging, as a sort of surgical tic or habit spasm; careless application of hæmostats, with painful indifference to the mass of crushed tissue left to necrose in the grip of the ligature—all of these constitute transgressions of which few of us can claim innocence. But they also constitute a prolific source of adhesions, and should therefore be constantly borne in mind in order to impress upon us the value and importance of diligently cultivating a healthy aversion to unnecessary trauma, and a profound respect for the tissues.

Coming now to a consideration of the prevention and treatment of adhesions certain prophylactic measures at once suggest themselves as being clearly indicated from what has already been said. Briefly stated these are—rigid asepsis; avoidance of mechanical, chemical or thermic trauma; careful covering up of all raw surfaces; use of hot moist gauze; and avoiding exposure of the peritoneum to the air. Thus far, practically everyone is agreed. But the common experience that troublesome and dangerous adhesions still quite frequently occur, in spite of the strictest possible observance of these measures, has stimulated investigators to undertake the most varied and elaborate researches with the hope of discovering some prophylactic or remedial agent that would prove efficacious in all cases. This work has resulted in the production of many ingenious and valuable procedures, all of which have at one time or another been enthusiastically advocated, and have received varying degrees of support from the profession generally. Most of them have been sufficiently tested now to admit of a pretty accurate opinion being formulated empirically, as to their actual worth. From a study of the numerous reports the following classification and valuation of these heterogeneous devices seems warranted.

1. *Non-Absorbable Protective Membranes.*—Under this caption may be included the covering of raw surfaces with collodion film; gelatin-formalin coagulum; lymph-aristol coagulum; silver foil; solution of gutta-percha in chloroform, carbon bisulphid, or xylol; and thin sheets of silk or rubber fabric.

None of these agencies can be relied upon to furnish more than a small percentage of uniform and successful results, and on this account, cannot be recommended for general use.

2. *Manual and Postural Arrangement of the Viscera.*—This is accomplished partly through proper disposal of the viscera with reference to normal anatomical relationship at the end of the operation, and partly through post-operative posture in the ward, with the double idea of avoiding permanent kinks at those movable parts of the gastro-intestinal canal which commonly produce untoward symptoms—such as the pylorus, upper part of jejunum, lower ileum, cæcum, transverse colon, and sigmoid—and for the further purpose of gravitating the abdominal contents away from raw surfaces. Both of these

procedures seem rational and worthy of more general consideration and use.

3. *Peristalsis.*—Considerable work has been done on the post-operative use of physostigmin, with the idea of stimulating strong peristalsis, and thus liberating early adhesions and preventing their recurrence. Conflicting results have been reported, however, and the routine use of this drug is of doubtful value.

4. *Specific Drugs.*—Iodides have been recommended with the idea that they inhibit proliferation of connective tissue, and aid in its absorption. Thiosinamin, and its combination wth salicylate of sodium, known as fibrolysin, have been accredited with possessing a softening influence upon cicatrices and other abnormal growths of connective tissue.

The use of various anti-fibrin ferments, with the intention of preventing coagulation of exuded serum—the first essential stage in adhesion formation—have been also tested experimentally and recommended. An encouraging increase of success has attended this pioneer work in an effort to apply specific chemo-therapy to the problem of peritoneal adhesions, and further development along this line is to be confidently expected.

5. *Normal salt solution* in large quantity poured into the abdomen at the end of the operation in order to float the loops of bowel into their normal relationship and keep denuded surfaces separated, was at one time extensively used. Later on adrenalin was added, with the idea of preventing exudate through its constricting action on the vessels. But it has been shown that absorption is too rapid to admit of much new growth of endothelium over raw surfaces before they again come into contact with adjacent tissues.

6. *Gases.*—Distention of the abdomen with oxygen gas just prior to closure of the peritoneum has been recently suggested as a useful resuscitating and anti-adhesion measure. So, too, intra-abdominal hyperæmia, brought about by periodic local application of the hot-air bath to the lower trunk has been recently quite warmly advocated.

7. *Eschar of the Thermo-cautery.*—As already indicated, if this measure is utilized, the cauterization should be very thorough, so as to form a deep and lasting charring of the tissues. This measure undoubtedly possesses distinct advantages under certain conditions.

8. *Lubricants.*—Because of their harmlessness, ease of application, and apparent effectiveness in many cases, various oily and fatty substances are perhaps more extensively used than any other single artificial measure in the treatment of adhesions. A number of substances of this kind have been suggested from time to time and carefully studied experimentally; including olive oil, vaseline oil, liquid lanolin, liquid petrolatum, and others. Vaseline oil seems to possess certain advantages, notably the fact that irritating fatty acids are not so readily split off from it during the process of sterilization, as is the case with olive oil. The sterilization should be carefully done, and the temperature not carried too high for this reason.

9. *Non-Viable Animal Membranes.*—Cargyle membrane, made from the peritoneum of the ox; a similar membrane from the shark's peritoneum; goldbeaters' skin, derived from the outer coat of the cæcum of the ox; and a fine woven cloth made of catgut, constitute the members of this group. Cargyle membrane has been more extensively used than any of these, but in the hands of some investigators it has given miserable results, and even its most enthusiastic advocates admit its failure in a number of instances. Theoretically, it is surprising that these membranes do not uniformly provoke, rather than prevent adhesions—and there is considerable experimental evidence in support of this view—inasmuch as a piece of dead animal tissue that has been kept in preservative fluids, although it may later undergo absorption, is in every sense of the word, a true foreign body while it remains in the peritoneal cavity, and must be so regarded in its relations to adhesion formation. It seems to me inevitable, therefore, that these substances will gradually fall into disuse.

10. *Viable Grafts.*—Much more rational are the efforts to cover raw surfaces by plastic operations on the peritoneum, or by autogenous grafts of omentum. It has been shown experimentally that if the entire omentum of dogs be amputated and simply dropped into the peritoneal cavity, it does not undergo necrosis, but on the contrary, quickly becomes spread out over the parietal peritoneum, to which it adheres, and promptly becomes vascularized.

Furthermore, it has been shown that omental grafts applied to denuded bowel surface establish sufficient vascular communication to admit of injection from the aorta with aniline fluids within the surprisingly short period of twenty-four hours. Again, no one has reported, as far as I know, an instance of necrosis of an omental graft. But unfortunately they do not prevent adhesions, except when applied to the abdominal parietes and to organs possessing strong peristalsis, such as the stomach and urinary bladder. On the small bowel they are very useful in reinforcing weak points and suture lines, but here they invariably adhere to neighboring loops.

It is evident, therefore, that grafts of fresh omentum and peritoneum have a very important and wide field of application, and it seems quite feasible to have at hand in the operating room, just prior to operations upon bad adhesion cases, an abundant supply of peritoneum obtained from a freshly slaughtered calf, under aseptic conditions, and carefully guarded from mechanical or chemical trauma, for extensive application.

A New Method of Treating Raw Bowel Surfaces.

A few months ago during the course of an operation for the relief of an enormous post-operative ventral hernia a situation arose which suggested to me a new, and what I believe to be an eminently satisfactory method of dealing with denuded bowel surface under certain conditions. The patient was a very large, fat woman, well past middle life, who, by reason of circulatory and renal disease, was rather a poor surgical risk. Moreover, about six months previously she had undergone a very serious operation for radical removal of the generative organs on account of a moderately advanced cancer

of the uterine cervix, at which time the abdominal wound had evidently become infected and broken down with a resulting hernia. Occupying the hernial sac, besides a bulky omentum densely adherent throughout, there was a long loop of ileum, coiled in a horse-shoe fashion, each limb of which had become so intimately adherent to the peritoneal lining of the sac as to render separation along any definite line of cleavage impossible. The two limbs were also adherent to each other by several transverse bands of dense fibrous tissue. After effecting the release of the intestine I had, therefore, two extensive raw areas, each measuring two to three inches in length, involving nearly one-half the circumference of the bowel, and separated from each other by six or eight inches of practically normal intestine.

Another factor of great surgical importance was the extensive dissection necessary to cure the hernia, by reason of the wide separation of the recti muscles, the enormous size of the opening, the abundant scar tissue produced by the old

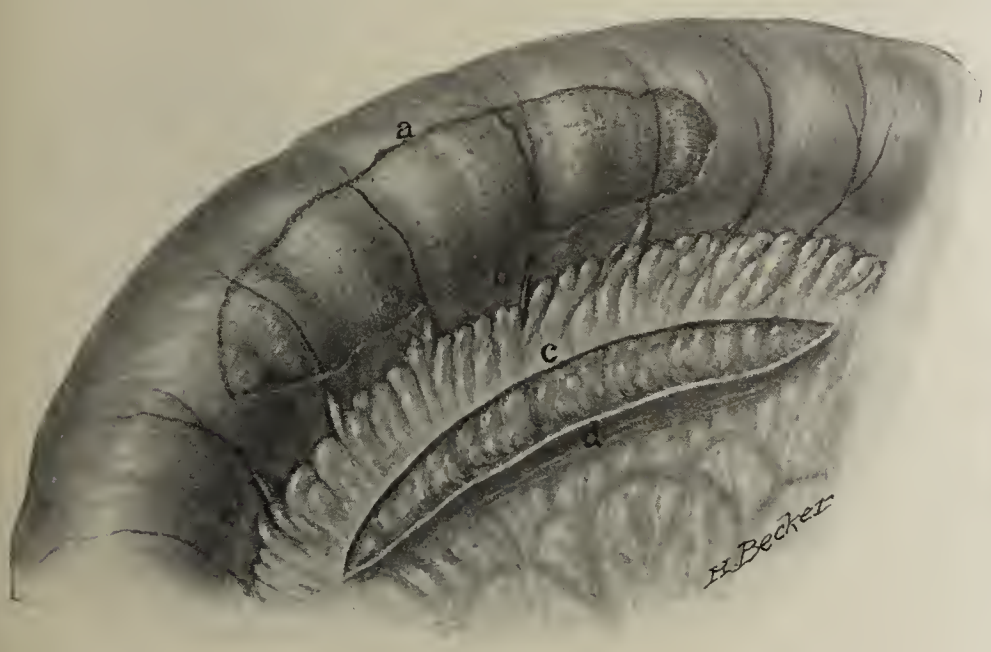


Fig. 1.—An extensive denuded area on the surface of the ileum is here shown. Observe that at its widest portion *a-b* it involves nearly one-half of the circumference of the bowel. The liberal deposit of fat in the mesentery here represented admits of the ready separation of its two peritoneal leaves. Note that the incision for this purpose through the upper leaf is made about 1 cm. from its bowel attachment, in order to avoid the numerous branching vessels in this region. The separation of the flap *d* is now easily and safely effected to any desired extent, since the average width of the mesentery is eight inches. A flat, blunt instrument—a spatula, for example—is best suited for this step. The rich vascular anastomosis between the mesenteric leaves, afforded by the superimposed colonnade arrangement of the trunk vessels, is easily seen.

infection, and the atrophy and impaired vascularity of the tissues to be utilized in effecting the closure. These unfortunate circumstances, together with the patient's general condition, made it highly important that all possibility of wound infection should be scrupulously avoided, as well as that every possible precaution should be taken against the occurrence of intestinal obstruction, which might necessitate the undoing of all my work. Now, recalling the condition of the bowel surface just described, it is evident, upon consideration, that none of the customary methods of dealing with this complication were applicable to the conditions in hand. I could not, for example, invert the raw surfaces, because of their extent and proximity to each other—obstruction would almost certainly have ensued. The various other measures already described were either impracticable or too unreliable, in view of the serious consequences of failure. I did not dare resort to lateral anastomosis, because I was dealing with the lower ileum; and while this procedure would have taken care of the raw surfaces and obviated the danger of obstruction, it would at the same time have afforded an excellent opportunity for infection of the devitalized tissues of the wound, with complete destruction of all my plastic work, and immediate recurrence of the hernia. Fortunately, the problem was practically solved for me by the accidental laceration and partial retraction of one leaflet of the mesenteric peritoneum just along its line of attachment to the bowel and adjacent to one of the raw areas on the surface of the latter, which occurred during its separation from the hernial sac (Fig. 1). There being a considerable deposit of fat between the two layers of

Fig. 2.—The detached flap of peritoneum is here shown drawn up over the raw bowel surface and firmly fixed by interrupted sutures of fine silk. Note how completely and satisfactorily the defect has been remedied. Observe too, that, owing to the mobility of both the bowel and its mesentery, the mechanical effect on the bowel lumen and the mesenteric circulation is negligible, and cannot produce any serious consequences. Care must be taken to close the angles of the mesenteric flap just at the bowel margin, as shown, to avoid the possibility of an intra-mesenteric hernia.

mesenteric peritoneum, it was a surprisingly simple and easy procedure to extend the separation of the torn leaflet and its attached fat in all directions from the underlying vessels and the opposite intact leaflet with its fat, thus obtaining a large movable flap of normal peritoneum which was easily drawn up without tension, spread out over the raw surface on the bowel, and tacked down with a few fine silk sutures (Fig. 2). The result was eminently satisfactory in every way, this very simple device, which was quickly carried out, having sufficed to abolish a rather complex and embarrassing surgical situation. The patient's recovery was complete and she is now comfortable and happy.

This fortunate experience led me to investigate the idea

further in order to determine accurately its limitations and to meet certain theoretical objections.

Thus it was desirable to ascertain if the method could be applied to all portions of the intestinal tract; if the separation of the two peritoneal leaves of the mesentery could be rapidly effected, without injury to the vessels in poorly nourished individuals whose mesentery usually contains very little fat; and if not, to consider the feasibility of lifting a fold of both leaves of the mesentery, without incising either, over the raw surfaces, thus effecting practically a plication of the mesentery—a modification of the method that would make it applicable to these cases also (Fig. 4); to determine further what effect this axial rotation, or partial envelopment of the bowel within its own mesentery, would have on the caliber and direction of the lumen, with reference to obstruction; to investigate to what extent it would be practicable to so treat

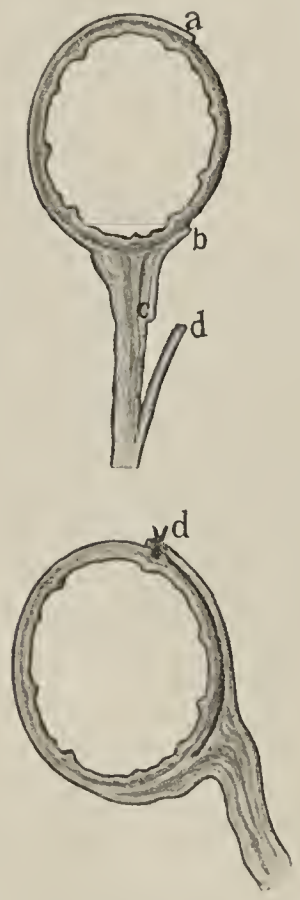


Fig. 3.—The bowel and its mesentery are here represented in cross-section. In the upper drawing, the area between *a* and *b* is the raw surface; *c* marks the point of incision through one peritoneal leaf of the mesentery; and *d* the flap to be freed and drawn up. The lower drawing shows the flap *d* closely applied over the denuded area, and fixed by sutures which should penetrate the submucosa.

the bowel, and to ascertain particularly what effect was produced on the mesenteric and bowel circulation by this mechanical alteration of normal conditions; and finally, how much tension the leaflet of mesenteric peritoneum is capable of withstanding, with reference to its being torn loose by postoperative distention or vigorous peristalsis.

The fresh cadaver seemed to offer the best method of settling these questions, and my conclusions, based upon such a study, are as follows:

1. The procedure is best applicable to that portion of the intestinal tract where, in such cases as the one described, present methods are inadequate, namely, from the upper jejunum to the lower ileum. It may be rationally applied, however, to any portion of the bowel possessing a mesentery of sufficient length to admit of its ready execution.

2. Care must be exercised at the duodenum, upper jejunum, and lower ileum not to produce kinks of the bowel.

3. In cases exhibiting a scanty deposit of fat in the mesentery, plication is a rapid, safe and efficient substitute for separation of the two peritoneal leaves.

4. Aside from a slight spiral rotation, which in view of peristalsis and the mobility of the parts is entirely insufficient to produce obstruction, the procedure has no demonstrable effect on the bowel lumen.

5. It can be safely extended to include nearly one-half the circumference of the bowel and three to four inches in continuity. There is no apparent reason why it should not be repeated as often as necessary at different levels of the intestinal tract.

6. In view of the rich vascular anastomosis and the mobility of both the bowel and its mesentery, if care be exercised in placing the sutures so as to avoid the trunk vessels, the effect upon the circulation is negligible.

Fig. 4.—The plication modification of the method is here shown. Owing to an almost total absence of fat between the peritoneal leaves of the mesentery in some cases, it is unsafe and impracticable to attempt their separation. In such cases *neither leaf is incised, or separated from its bowel attachment*, but both leaves are grasped together at the proper distance from the bowel border, lifted over the raw surface and fixed by silk sutures. It amounts to a plication of the mesentery, or a partial envelopment of the bowel within both layers of its mesentery. Note that care has been taken to place the sutures between the vascular trunks. This simple modification renders the method applicable to all cases, is even more quickly executed, and is eminently safe and satisfactory.

7. Stability and permanence of the coaptation is readily secured through intelligent disposition of the sutures.

Summary.

Certain anatomical and physiological characteristics of the peritoneum have an important bearing on the problem of peritoneal adhesions. Notably its area, its absorptive power, the variable sensitiveness to pain of different portions, the continuity of its epithelial surface, the rapidity with which it can form adhesions, and the completeness with which it can later absorb them.

Injury or death of the highly vulnerable surface endothelium is sufficient to set in motion the chain of pathological events which terminates in dense adhesions with scar tissue formation.

Etiologically there are a number and variety of factors involved, but they can all be grouped under the two heads, *Sepsis* and *Trauma*.

As prophylactic and curative measures, emphasis should be given to rigid asepsis, the use of moist hot gauze, careful covering of all raw surfaces, avoiding unnecessary exposure, restricting trauma and spreading out of the omentum over the visceral surfaces before closing the abdomen.

A number of additional safeguards are available which have been tested and proven to be of value under certain conditions: the most valuable of these for general use are lubricants, viable grafts of peritoneum, or omentum and judicious ante- and post-operative therapy.

The field of specific chemo-therapy offers the brightest hopes for future progress.

In properly selected cases the use of adjacent mesentery for covering raw bowel surfaces possesses distinct advantages over all methods hitherto proposed.

I desire to express my thanks to the pathological department of The Johns Hopkins Hospital for giving me the opportunity of testing, on the fresh cadaver, the method above described.

PRIMARY CARCINOMA OF THE PLEURA.

By T. P. Sprunt, M. D.,
Instructor in Pathology, The Johns Hopkins University.

The primary malignant tumors of the pleura, although rare, have considerable interest for the clinician on account of the difficulty encountered in attempting an accurate differential diagnosis. They have their principal interest, however, from the point of view of their pathology; and not only does this interest attach to the question of histogenesis but to their ultimate nature and origin. Doubts have been expressed as to whether we are dealing here with a true tumor in the narrower sense of that term or whether the lesion may not be the result of the chronic inflammatory process which so uniformly accompanies it.

The classical pleural tumor was first described by Wagner and later by his pupil Schulz, and called by them endothelial cancer. The pleura was much thickened and somewhat roughened, resembling the appearance seen in the mucosa of the bladder with prominent, hypertrophic musculature. Histologically the growth in the thickened pleural tissues consisted of numerous alveolar and tubular structures separated from each other by a connective tissue stroma and filled with large epithelial-like cells. They considered the endothelium of the lymph vessels the point of origin of the growth.

A number of cases have since been reported. Glockner, in 1897, collected 42 cases from the literature and added 7 of his own. Gutmann, in 1903, found 9 additional cases. In 1905 Bloch collected 47 endotheliomata and 16 sarcomata.

The individual authors, as a rule, compare their cases with the classical Wagnerian tumor which most of them closely resemble. The tubules and alveoli are sometimes filled with cells, at other times the spaces are lined by cubical or cylindrical cells in one or many layers. Practically all agree that the cells strongly resemble epithelial cells and that the histological picture is that of carcinoma, but the great diversity of opinion as to the nature of the affection may be easily appreciated after a mere enumeration of the names, which have been given it. Among these designations we may mention that of endothelial cancer (Schulz, Wagner, *et al.*), lymphangitis prolifera (Fraenkel, Schweninger), lymphangitis carcinomatodes (Neelsen), sarcocarcinoma (Boehme), alveolar endothelial sarcoma (Padock), endothelioma (Eppinger and many others), carcinoma (Lepine, Pitt, Benda, Dreesen, Ribbert, Orth).

In most of these reports the lining membrane of the pleura was either entirely lost or its cells, if present, only slightly changed. The great majority of the authors refer the point of origin of the tumors to the endothelial lining of the lymphatics.

Benda reports a case in which the principal growth occurred on the pleural surface which was covered with numerous villi. The picture reminded him of the formation of papilli in certain ovarian cystomata. These villi were covered by cylindrical cells and possessed a stroma of connective tissue and blood vessels or occasionally granulation tissue. In the depth, there were many alveoli and strands of epithelial cells or else glandular formations and even small cysts which occasionally showed papillomatous projections from their walls. He considers as true epithelium the cells covering the pleura and his tumor, therefore, as a true carcinoma. He could come to no decided opinion as to the participation of the lymph vessel endothelium, but was inclined to regard the tumor masses in the subpleural tissues as extensions downward from the growth on the pleural surface.

Dreesen reports a similar case and reaches similar conclusions. They are both of the opinion that many of the reported cases had a like origin.

In connection with tumors of the serous surfaces there has been much discussion concerning the embryological development of the serous lining membranes, and concerning the classification of their cells. In the older literature the term endothelium is used almost exclusively, but in recent years many authors consider these cells more closely allied to epithelial structures than to the endothelium and consequently prefer to speak of them as epithelium. Malignant tumors aris-

ing from these cells therefore, they say, should be called carcinomata.

It is now generally held that in their embryology these cells have nothing in common with the endothelial lining cells of the blood and lymph vascular systems. In addition, it has been shown that in certain of the lower vertebrates, the body cavity originates as an invagination of the hypoblast, but there is no sign of such an invagination in the higher vertebrates, in which the body cavities seem to originate by a splitting of the mesoblast with subsequently a differentiation of some of its cells into a lining membrane.

From studies of their behavior under pathological conditions, Mönekeberg, Büttner, Hinsberg, Herxheimer, v. Brunn, and others conclude that the lining cells of the body cavities have more in common with epithelium than with endothelium and the connective tissues. Opposite opinions are expressed by Ranvier, Roloff, and others who conducted somewhat similar experiments. Beitzke, Orth, and Ribbert among other eminent pathologists speak for their epithelial nature.

If then we choose to speak of these cells as epithelium we must regard them as epithelial cells of mesoblastic origin, and related in this respect to the epithelium of the adrenals, kidneys and other organs of the urogenital tract including perhaps that of the uterus and vagina. Most classifications of tumors leave those arising from these organs in a sad state of disorder and it is especially in tumors of this type that Adami's classification seems superior.

In a recent article on pleural tumors Ribbert gives his opinion that the so-called endotheliomata of the pleura are not derived from the endothelium of the lymph vessels, but either from the surface epithelial cells or from misplaced epithelium, and that they should be termed carcinomata. However, he says that such an origin has not yet been proved beyond doubt in a single case, since sufficiently early stages have not been observed.

The tumor described in this report can hardly be regarded in any other way than having arisen from the epithelial lining of the pleura. Its histology in no way resembles that of the classical "endothelial cancer," and it has many points of departure from those described by Benda and Dresen.

Clinical History.—Mrs. ——, a white woman, was a private patient of Dr. Thomas R. Brown, to whom the author is indebted for the clinical notes.

She was admitted to the Church Home and Infirmary, March 22, 1910, about two and a half weeks after the onset of her terminal illness, with extreme pain in the left chest and abdomen, some nausea and vomiting, and persistent cough.

Of interest in the *family history* is the fact that her mother died of carcinoma of the uterus.

In the past the patient had been strong and well physically, but, married to a confirmed drunkard, she had been subject to great nervous strain and at times was the victim of physical violence. A few years before the onset of the present illness a laparotomy had been performed by Dr. H. A. Kelly and the appendix, right tube and ovary removed. Examination of the specimens showed a chronic inflammatory process, but no evidence of neoplasm.

When she entered the hospital the physical signs were typical of a pleural effusion on the left side. The heart was pushed over to the right parasternal line. The point of maximal impulse was difficult to determine, but there was a distinct impulse half way between the parasternal and sidesternal lines on the left side. The whole of the left chest showed absolute flatness and loss of vocal fremitus. The breath sounds were absent over this area except in the upper left front, where they were distant, harsh and of broncho-vesicular type.

The spleen was palpable. The liver, also, was readily felt, but perfectly smooth and not tender on pressure.

No tubercle bacilli could be found in the sputum. The urine, stools and stomach contents were normal. Rectal examination revealed nothing abnormal. The blood count showed 27,000 leucocytes and 3,500,000 red blood cells.

The left thorax was tapped 14 times and an average of a little over 2000 cc. of fluid aspirated each time. In all 28,270 cc. were removed: the largest amount aspirated at any one time was 3150 cc. The fluid was always gelatinous, varied in color from a pinkish-straw to cherry red, and occasionally contained small bits of fibrin. There was between 1 per cent and 2 per cent of red blood cells and many leucocytes with a great preponderance of neutrophiles. No cells nor fragments suggesting a new growth were observed. Cultures from the fluid remained sterile and stained smears showed no organisms. Inoculation of a guinea pig also proved negative.

The relief after each tapping was slight and lasted only a short while. On each occasion there was a remarkable shifting of the heart's position from 4 to 6 cm. without any change in the pulse rate.

During the first month in the hospital, the temperature and pulse curves were about normal. The temperature during the last 3 weeks was intermittent, from 97° F. to 102° F. or 104° F. and the pulse varied from 100 to 130. The pain in the chest and dyspnœa were often very distressing and there occurred at intervals marked abdominal symptoms, as nausea, vomiting and pain. Cough was never a prominent feature and there was little sputum. On one occasion shortly after tapping a small quantity of bright red blood was expectorated.

The subjective symptoms increased in severity and less and less relief was experienced after the tappings which occurred at more frequent intervals. The patient died apparently from asthenia *ten weeks* after the appearance of the first symptoms.

The physical signs of extreme pleural effusion, the hemorrhagic character of the exudate, the lack of relief after aspiration, the rapid reaccumulation of the fluid, the negative bacteriological tests and the progressive cachexia led to the clinical diagnosis of malignant growth of the left pleura. Whether the growth was primary or secondary could not be determined.

The autopsy (J. H. U. Path. Lab., 3386) was performed two hours after death.

Anatomical Diagnosis.—Primary carcinoma of left pleura; extension to left lung and bronchial lymph nodes; serofibrinous pleuritis (left); total atelectasis of left lung; hydropericardium; right hydrothorax; hypostatic œdema and congestion of right lung with some atelectasis of lower lobe; thrombosis of uterine plexus; pulmonary emboli; chronic passive congestion of spleen; fatty degeneration of heart musele and liver; anemia; cachexia; scar of old laparotomy (right salpingo-oöphorectomy and appendectomy); chronic pelvic peritonitis with adhesions to sigmoid and ileum; dilatation of stomach and duodenum.

The body is that of a well-nourished white woman. The skin is of a lemon-yellow color, especially marked over the face and hands. The mucous membrances and finger nails are decidedly pale. The muscles are flabby. There are no glandular enlargements in the neck, axillæ or inguinal regions. The breasts are symmetrical, are not pendulous, there is no great excess of fat, no lumps, or any demonstrable abnormality. There is a linear median scar in the lower part of the abdomen. The fat of the abdominal wall is about 1 cm. in thickness and has an orange color. The peritoneal surfaces are normal; there is no free fluid. The stomach and duodenum are greatly dilated. The liver extends about 5 cm. below the costal margin in the right mammillary line and to a point about 4 cm. above the umbilicus in the median line. The diaphragm on the left side has been pushed down until its abdominal surface is convex instead of showing the usual dome-like concavity. On the right the diaphragm reaches the fifth rib. Its peritoneal surfaces are smooth on both sides. The mesenteric lymph nodes are not enlarged. About two feet above the ileocæcal valve a loop of the ileum descends into the pelvis and is adherent to the posterior wall of the uterus. A loop of the sigmoid flexure is also adherent to an inflammatory mass around the left ovary.

Thorax: On removing the sternum there is a gush of turbid, straw-colored fluid from the left pleural cavity which is filled with this material. The right pleura contains about one litre of slightly cloudy fluid. The pericardium also shows a considerable excess of fluid. Its surfaces are smooth, although the parietal wall seems somewhat thickened.

The heart, which was displaced to the right, weighs 250 grams. There is a slight excess of lemon-colored, subepicardial fat, and on tangential section the muscle is slightly mottled with yellowish specks.

Lungs: The right lung is entirely free from adhesions. Its surfaces are smooth and glistening. The upper and middle lobes are slightly moist and show a moderate grade of compensatory emphysema. The tissues of the lower lobe are distinctly more moist and more congested and show in addition partial atelectasis. The small arteries contain reddish, friable thrombi which protrude from the lumen on the cut surface.

The left pleural cavity is filled with several litres of cloudy fluid in which float strands and filmy sheets of a very friable material. This substance lines the whole pleural cavity in veil-like layers, is quite soft, of a pinkish-gray color and can be easily scraped off with the fingers. When this is removed from the parietal wall a harder tissue is revealed which is roughened by small, thickly set nodules about the size of a pea and smaller. This appearance is especially striking on the parietal pleura opposite the third, fourth, fifth and sixth ribs.

The lung is reduced to a fusiform swelling along the left side of the mediastinal tissues and projecting only about 3 cm. into the pleural cavity. It is covered by the friable shreddy material already described. On incision of the lung there is found immediately beneath the fibrinous exudate a thin, apparently fibrous layer. Beneath this the lung substance is green in color, completely collapsed and airless with small black specks scattered throughout. Here and there appear elevated nodules of a bluish-white tissue. These nodules are about 1 cm. in diameter, but occasionally fuse into larger areas measuring 2½ cm. All of them are superficial and near the pleural surface. They are flecked with numerous, yellow and black specks. The left side of the diaphragm shows also the upper surface of fibrinous material, a layer of white tissue measuring about 2 or 3 cm. in thickness, beneath which is a very pale muscle layer 5 mm. thick and showing here and there white streaks. The costal pleura is easily stripped off in some places, but in others is quite firmly bound to the thoracic wall. Section through the nodular area already mentioned shows that some of these nodules are 1 cm. in thickness, of a bluish-white color, firm consistence, with many tiny, opaque, yellow and yellowish-white flecks. The bronchial and peritracheal lymph nodes are enlarged and black. The surface of a few of those nearest the diseased pleura is covered by a rather thick bluish-white layer which extends down into the lymphatic tissue. The trachea and bronchi are somewhat congested, but are otherwise normal.

The axillary lymph nodes on the left side are not enlarged nor of increased consistence. Incision through the breast tissue shows nothing abnormal.

The œsophagus and aorta are normal.

The spleen is enlarged, weighing 250 grams. The surface is dark purplish-gray in color. The organ is very firm with a dark purple, smooth, cut surface.

The stomach and duodenum are considerably dilated and their mucosa digested, but otherwise the gastro-intestinal canal shows nothing remarkable.

The liver weighs 1400 grams, measuring 26 x 19 x 10 cm. Multiple sections show nothing unusual.

The pancreas, adrenals and kidneys are practically normal, although somewhat pale.

Pelvic Organs: The rectum is normal. The left uterine appendages are bound together and to the posterior wall of Douglass' pouch by old fibrous adhesions. The right appendages and appendix had been removed at operation. All the radicles of the venous plexus on each side of the cervix uteri contain cylindrical, reddish, friable casts. The retroperitoneal lymph nodes are somewhat enlarged, pink in color and slightly increased in consistence.

The neck organs and brain were not examined.

Microscopical Notes.—Sections through the nodular portion of the costal pleura show the subpleural tissues thickened and infiltrated with small round cells (Figs. 1-4). The nodules described in gross show the histological appearance typical of carcinoma. There are very rarely any tumor cells in the subpleural tissues, but toward the pleural cavity there extend up numerous finger-like projections having a stroma like that of the sub-pleural tissues and covered by a single layer of columnar epithelium. These processes anastomose quite freely, and in this way form spaces of various sizes and shapes which are lined by one or more layers of columnar cells. Between the nodules the pleural membrane is preserved in many places. The cells show various stages of proliferation. For the most part the cells are columnar in shape, and there are frequent small villi covering the pleural surface (Figs. 3-4). Occasionally the pleural lining is straight and regular consisting of cubical cells (Figs. 1-2), or even flat cells having much the appearance of the normal lining cell (Fig. 6). The transitions may be traced from this regular arrangement to the complicated papillomatous nodules already described. Not only is the pleural surface covered with many villous projections, but these occur regularly in the cyst-like spaces of the larger tumor nodules giving the picture of an intracystic papilloma (Figs. 1, 3, 4, 5).

Near the base of these nodules this cystic and papillomatous structure is most marked. The cells are of a high columnar type with large vesicular nuclei (Fig. 6). Usually there is a single layer, but at times they are piled up several cells thick. In the more superficial parts of the tumor, the papillomatous projections are less marked, and the spaces are being filled up by proliferation of the epithelial cells (Fig. 7), so that here and there they appear as solid strands of epithelial cells, separated by narrow bands of stroma giving the typical appearance of carcinoma simplex (Fig. 8). The free surface of the tumor is covered by a thick layer of fibrin and leucocytes with many red blood cells. Below this there is a very cellular granulation tissue which forms the stroma for the more superficial parts of the tumor. Occasionally the tumor is seen beneath the former line

of the pleura in the subpleural tissue. Here it takes the form of a small cyst-like structure with papillomatous projections into its cavity (Fig. 4). These are lined with quite regular high, columnar epithelium. Similar structures are found occasionally in the fibrous layer over the diaphragm. The muscle of the diaphragm is infiltrated with the elements of the acute inflammation, is quite œdematous, but shows no infiltration by the tumor.

Sections through the lung and visceral pleura show on its surface an acute inflammatory exudate and beneath this a thick layer of granulation tissue (Fig. 9). There is no sign of the original pleural lining. Along the superficial surface of the lung there are masses of the tumor quite similar to the areas already described, appearing as larger or smaller cystic structures with papillomatous lining (Fig. 11). Many of the larger ones show granular necrotic contents. The tumor cells like those on the costal pleura are cylindrical with vesicular nuclei and fairly regular appearance, although here and there several layers are seen and an occasional dark, irregular nucleus. Dipping down into the atelectatic lung there are larger tumor nodules which have a somewhat different appearance. These have much the same general arrangement with thin, anastomosing strands of stroma lined by columnar cells of irregular shape and size, giving a much more malignant appearance (Figs. 9, 11, 12). There is no sharply defined line between these tumor masses and the lung tissue, but little tongues of the tumor extend in between the tissues of the collapsed lung in a definitely invasive manner (Fig. 12.) The bronchi within the lung seem quite regular and normal.

In other sections of the visceral pleura and lung, instead of the large areas along the former pleural line there are small spaces from 15 to 30 microns in diameter lined by similar cylindrical or cubical cells (Fig. 9, 10). In these sections the portion of the tumor invading the lung resembles those already described.

Left bronchial gland: The metastasis here is quite similar to those in the lungs—the cells, however, are not quite so irregular in appearance, and there is more of a tendency in proliferating to fill up the alveolar space, forming solid strands of epithelial cells. The basement membranes of the gland-like structures are very indefinite (Fig. 13).

Other lymph nodes, mesenteric, axillary, retroperitoneal and higher peritracheal nodes show no metastases.

Mitotic figures are rarely seen in the more typical papillomatous areas at the base of the parietal nodules and on the surface of the lung. They are readily found in the more superficial portions of the nodules and are quite numerous in the extensions into the lung tissue.

In summary we have a large number of nodules on the parietal pleura consisting of a papillomatous growth with cylindrical cells covering the connective tissue strands. At the edge of such nodules we find villi projecting from the pleural surface forming a transitional stage between the more conspicuous growth and the flat pleural surface. Selective stains show the usual layer of elastic tissue beneath the pleura, although the fibers are much stretched and quite atrophic. This gives additional evidence, if any is needed, that the membrane in question is really the serous covering of the pleura. Just below the line of the pleura there occur occasionally small, cyst-like structures resembling the basal portion of the surface nodules. These are found in other parts of the parietal pleura, which do not show the lining membrane, and along the surface of the lung. In close association with these regular, adenomatous areas begin the extensions into the lung substance, which have a less typical histological appearance (adeno-carcinoma) and show definitely invasive growth in the deeper portions.

The objection may be raised that such a picture might be afforded by the extension of a bronchial cancer to the pleura. This view has been given careful attention. All the evidence is in favor of a primary pleural tumor extending into the lung. There is none favoring a bronchial origin. In many sections from different blocks the bronchi seem perfectly normal. The portions of the tumor within the lung are, as a rule, triangular in shape with the base at the surface and apex in the depth. All are in direct connection with the growth on the surface of the lung and transitions from the adenomatous tumor on the surface to the adeno-carcinoma within the lung are evident in most of the sections. The cells at the apices of the lung nodules lose their gland-like arrangement and infiltrate the atelectatic lung as solid, slender strands of epithelial cells.

We may reach the conclusion that we have a tumor, whose cells are in general atypical, arising from epithelium of mesoblastic origin. However, it retains throughout its epithelial nature, never reverting to the connective tissue type. If we adopt Adami's phraseology, we should speak of it as a transitional lepidoma or a mesothelial carcinoma, since it arises from what he calls a transitional lining membrane or epithelium of mesoblastic origin.

Since it varies so markedly from other reported pleural tumors, we are not justified in making any broad generalizations. We should expect tumors of such origin to show many variations.

EXPLANATION OF FIGURES.

1. Edge of one of the nodules on costal pleura. Leitz, Obj. 2, eyepiece 1.

2. Higher power of pleural epithelium shown in Fig. 1. Obj. 4, eyepiece, 1.

3. Villi on costal pleura between two larger tumor nodules. Obj. 2, eyepiece 1.

4. Costal pleura between two nodules. Shows the neoplasm also in the subpleural tissues. Obj. 2, eyepiece 1.

5. Base of a large costal nodule. Subpleural tissues shown in lower part of figure. Intracystic papilloma. Obj. 2, eyepiece 1.

6. Higher power of part marked x in Fig. 5. The lower epithelial line corresponds in position to the serous covering of the pleura. Obj. 4, eyepiece 1.

7. From more superficial portion of same nodule shown in Figs. 5 and 6. Proliferation of cells tending to fill up the spaces. Obj. 4, eyepiece 1.

8. From highest point of nodule shown in Figs. 5, 6 and 7. Advanced stage of process shown in Fig. 7. Solid epithelial nests separated by connective tissue strands. Obj. 4, eyepiece 1.

9. Visceral pleura with extension of tumor into lung. Acute exudate on surface, below which is a layer of granulation tissue, then small spaces lined by tumor cells, which extend further into the lungs as an adenocarcinoma. Note atelectatic lung in lower left corner of figure. Obj. 2, eyepiece 1.

10. Higher power of part of Fig. 9. Obj. 4, eyepiece 1.

11. Nodules on surface of lung More regular adenomatous structure with papillomatous projections into lumen (upper right of figure). Tumor cells of less typical structure invading atelectatic lung (lower left). Obj. 4, eyepiece 1.

12. Deeper portion of adenocarcinoma invading atelectatic lung. Obj. 4, eyepiece 1.

13. Metastasis to bronchial lymph node. Obj. 4, eyepiece 1.

FIG. 2.

FIG. 4.

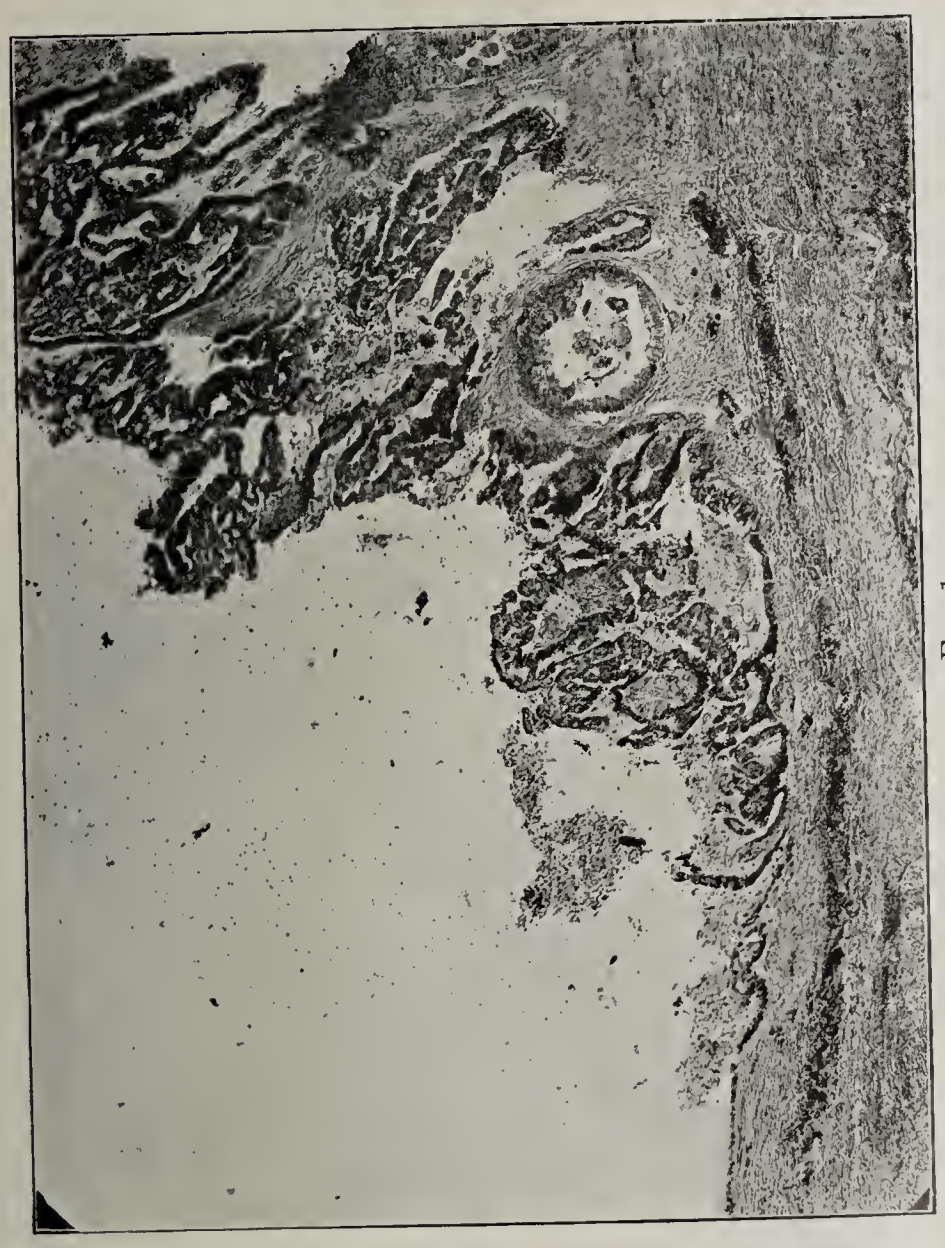
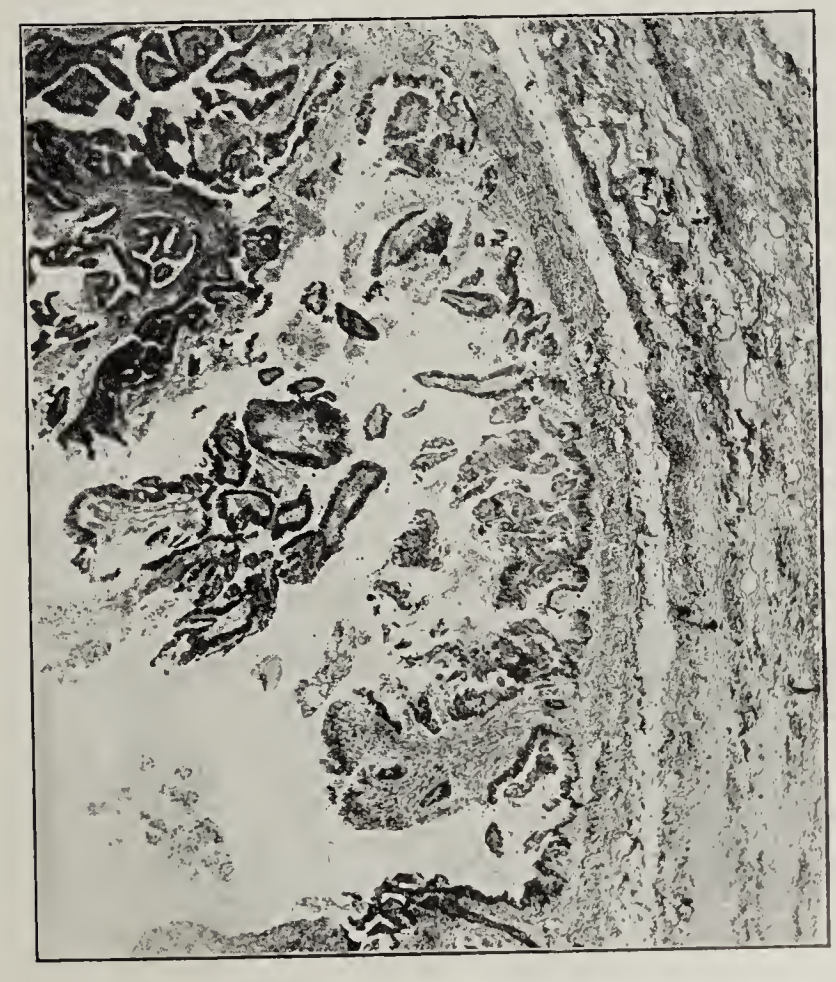


FIG. 1.



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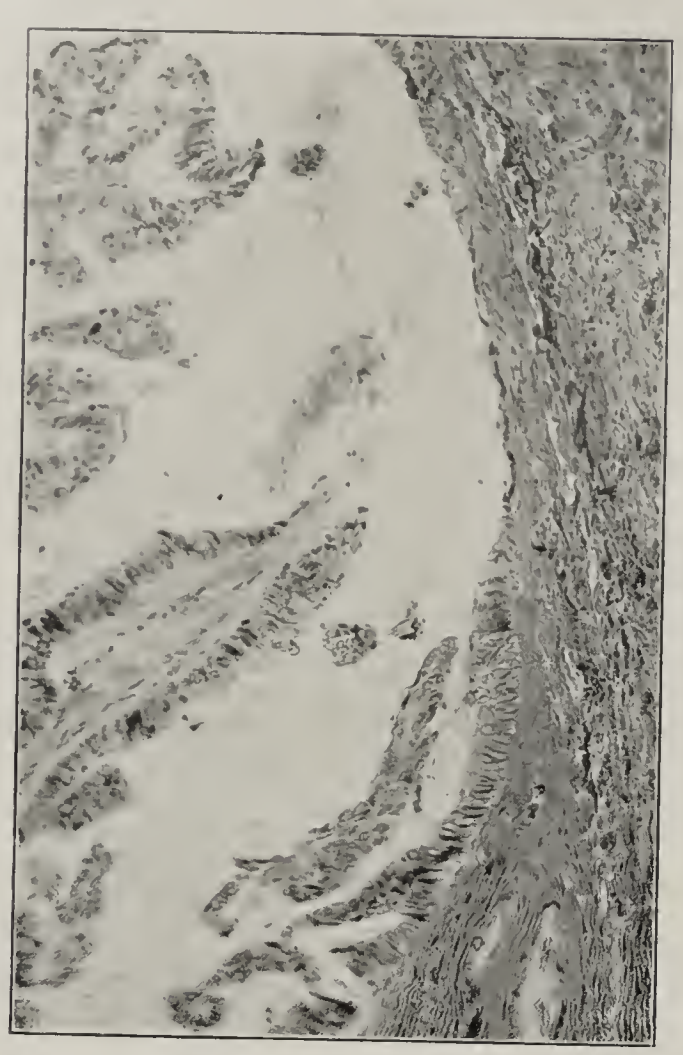

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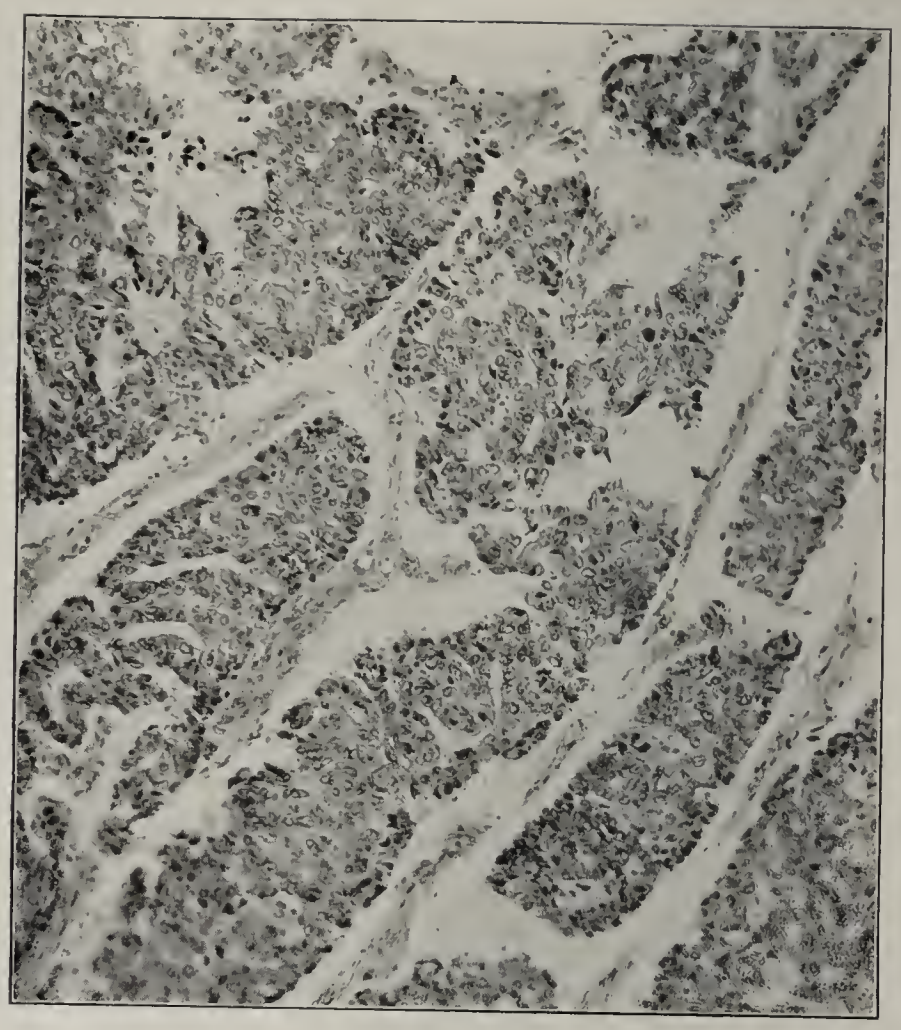

FIG. 8.

FIG. 5.

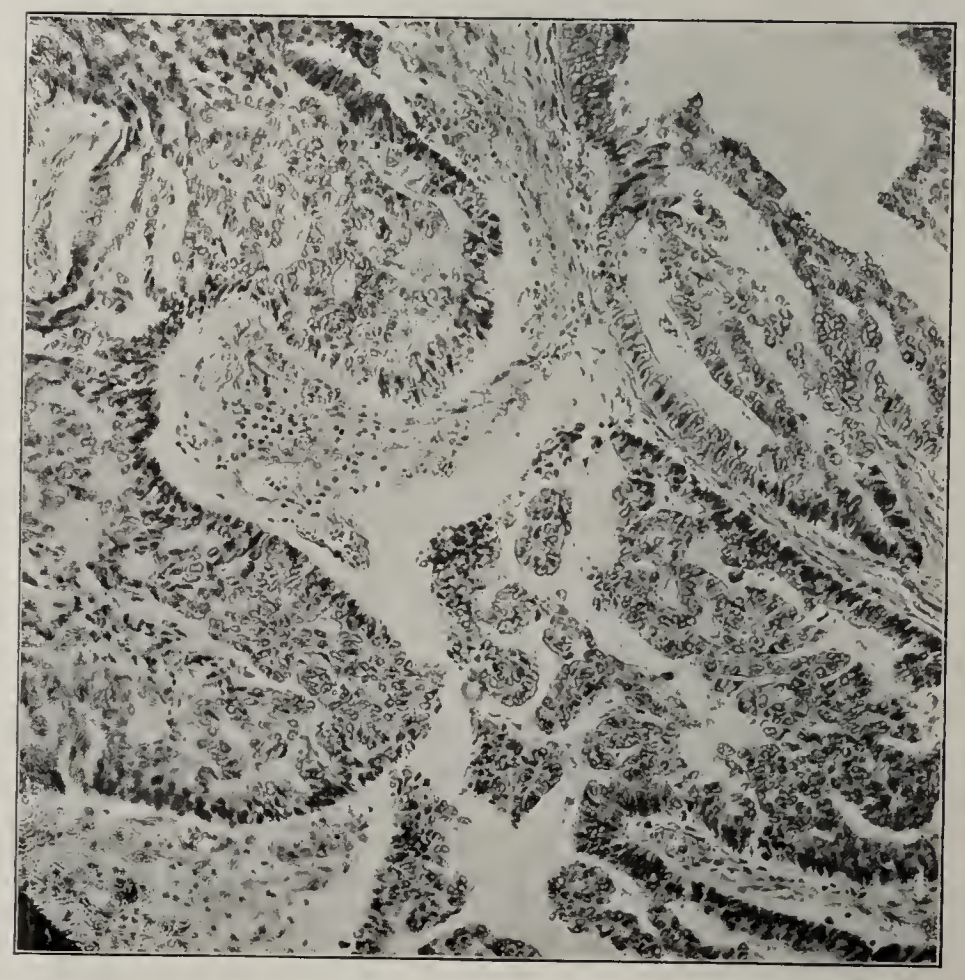

FIG. 7.

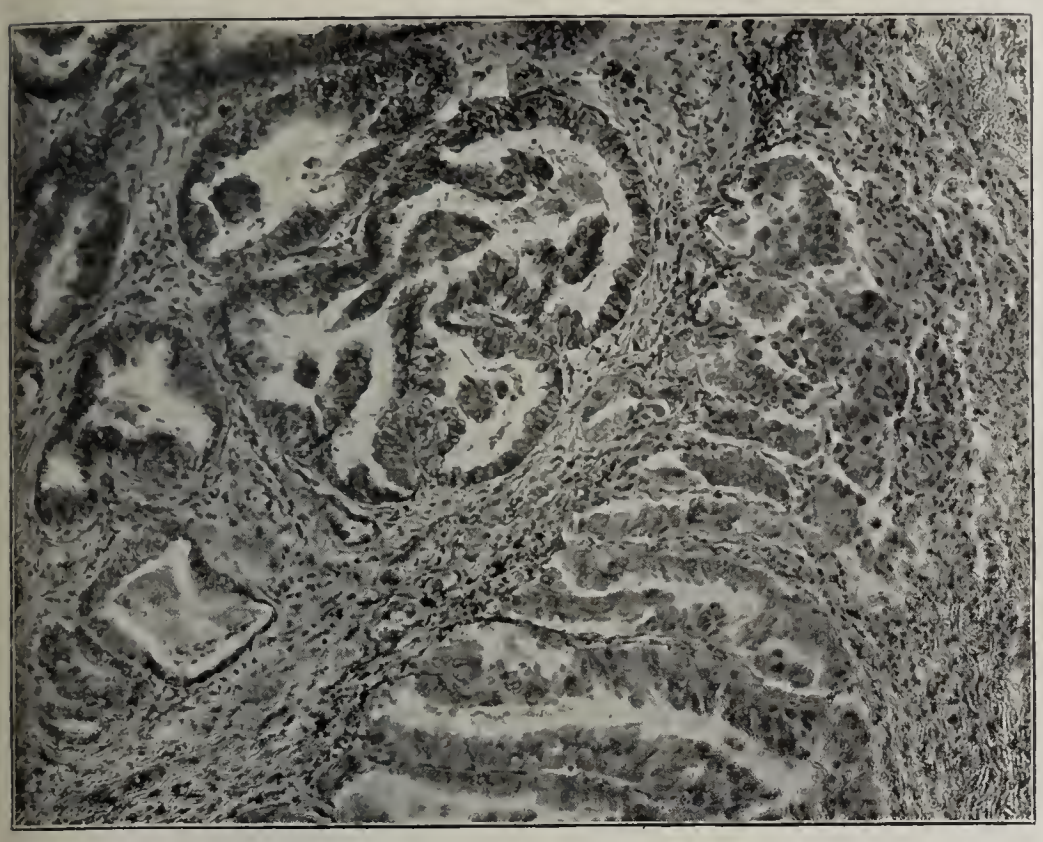

FIG. 11.

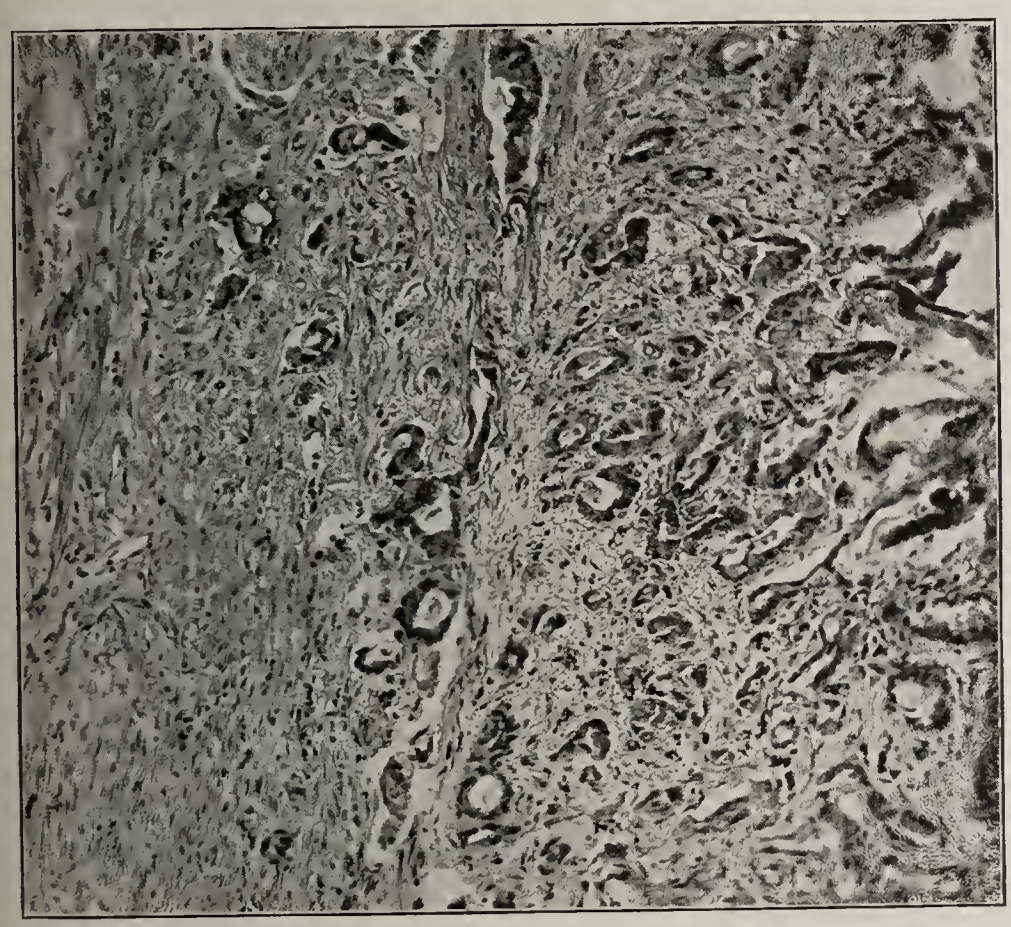

FIG. 10.

FIG. 9.

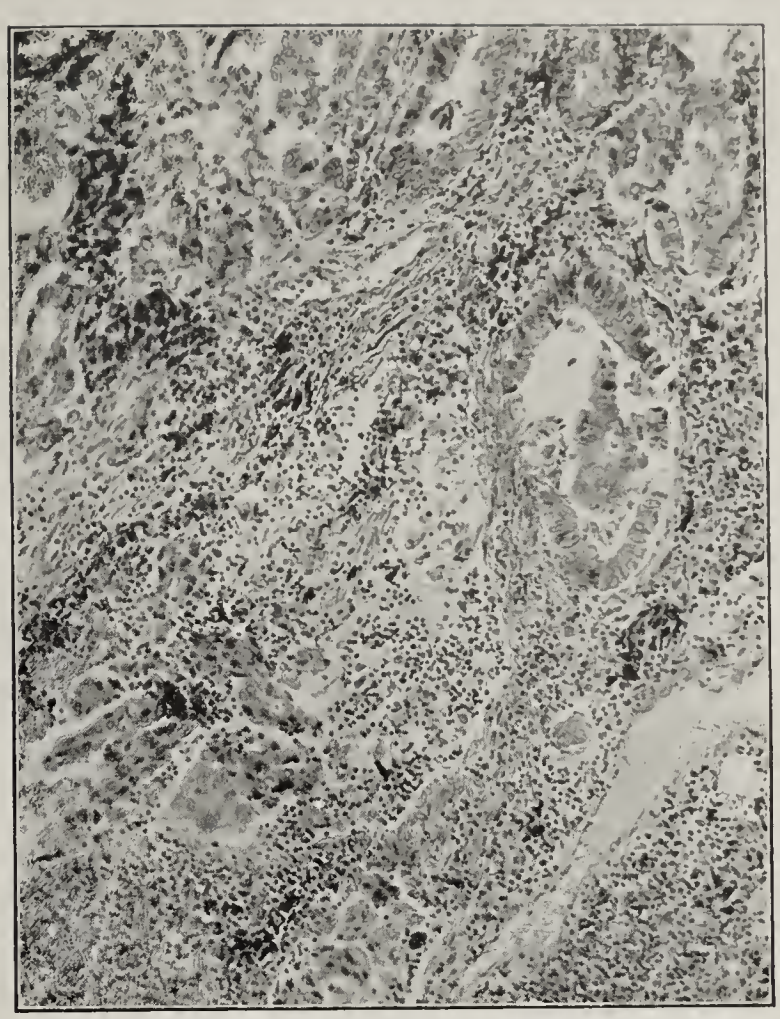

FIG. 13.

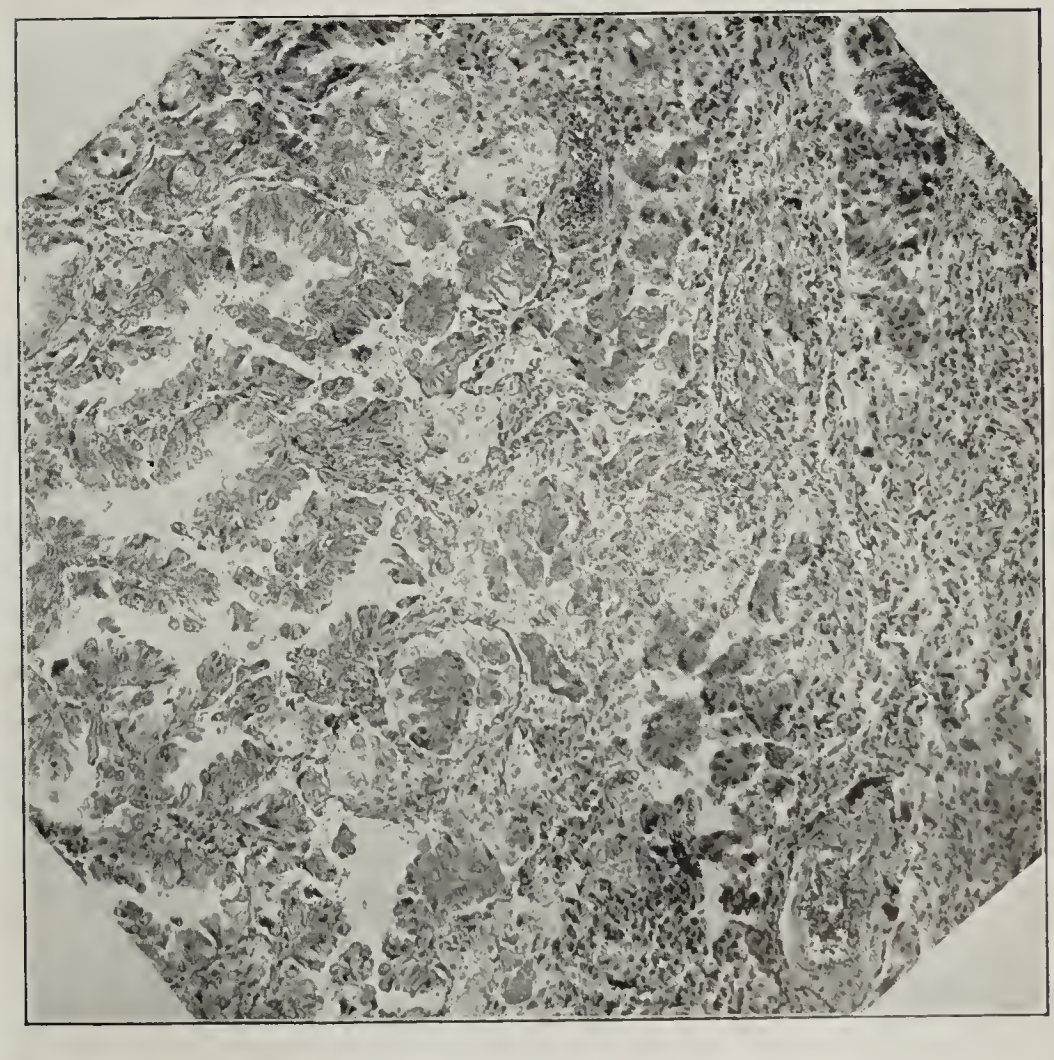

FIG. 12.

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REPORT OF A CASE OF PUERPERAL INFECTION WITH ISOLATION FROM THE UTERUS OF *B. INFLUENZÆ* AND A NEW METHOD FOR MAKING BLOOD AGAR FOR ITS CULTIVATION.

By WILLIAM THALHIMER, M. D.

(*From the Pathological Laboratory of the University of Virginia.*)

Since the discovery by Pfeiffer in 1892 of *B. influenzæ* along with methods for its cultivation and recognition, the wide-spread occurrence and importance of this organism have everywhere been recognized. At first it was believed to affect only the respiratory tract, but many cases are now on record of meningitis, endocarditis with bacteræmia and middle ear disease due to this bacillus, which has also been recovered from an infected gall bladder by Kinna and by Heyrovsky, and from the urethra by Cohn. A search of the literature has revealed, however, only one case where this bacillus was recovered from the female genital tract. This is a case reported by Kiskault under the title "Influenzabacillen bei Pyo- und Hydro-Salpinx," and is briefly as follows:

History.—Frau E., 40 years old, married 14 years, sterile. Nine years ago the patient was operated on for disease of the right ovary.* Since then has been troubled off and on with dysmenorrhœa. Has been under observation for three and a half weeks, and since yesterday has had severe abdominal pain, and since last night has had slight bleeding from the uterus.

Status.—Uterus small, ante-dextroposed, resting upon the symphysis, and behind it is a massive exudate.

Operation.—April 22, 1905. Posterior vaginal incision with thermocautery and opening of both sides of exudate. From right side flowed pus and from the left bloody serum. Drainage inserted. April 26, drainage removed. Slight discharge, a little pus. May 22, dilatation of opening. June 6, discharged. Uterus ante-flexed, still a slight exudate to right. Slight discharge.

Microscopic examination of pus showed many extra-cellular, minute, Gram negative bacilli. A small number of the same were found in the fluid from the exudate of the left side.

There was a typical growth of colonies of influenza bacilli on blood-streaked agar and the same on agar smeared with pus. No growth, however, in bouillon and plan agar. Subcultures were easily grown on blood agar.

Additional History.—On further questioning, the patient said she had an attack of influenza eight or nine years previously, but none since then.

* The nature of this ovarian disease is not stated and therefore the possible relationship between it and the attack of influenza, mentioned in the additional note, cannot be determined.

In light of this solitary finding in the literature the following case seems worthy of being placed on record.

Mrs. ———. Thirty-one years old. Admitted January 19, 1911.

Family History.—Negative, except that about one year ago the patient's husband was treated at the University Hospital for an acute unilateral gonorrhœal epididymitis, the gonococci being found in smears.

Past History.—Usual children's diseases and a severe attack of influenza 15 years ago when the patient was 16 years old. This lasted for two weeks, with pains in limbs, cough and purulent expectoration, but the patient was not forced to take to bed. There has been no attack of a similar kind since then, but patient is prone to catch cold, having several attacks every winter. Genito-urinary history negative, menstruation normal, never any abdominal pain. Patient has one child two years old; this pregnancy, labor and puerperium were normal.

Present Illness.—Four days ago after a normal pregnancy, patient passed through a normal labor, and felt tolerably well after the child was born, not feeling badly till three days afterwards, when she was troubled with a severe pain in the lower abdomen. She had no chills at this time but later in the night had several, and after each one felt feverish. The next day a physician was called who advised her to enter the hospital.

Status Præsens.—On admission patient's temperature was 105.4° F., pulse 140, respiration 30, and leucocytes 12,400. Except for tenderness in lower abdomen, especially on right side with slight muscle spasm, physical examination was negative. No mass could be felt.

Local Examination.—Patient taken to operating room, prepared for vaginal examination. Culture taken from uterine cavity on plain agar. Uterine cavity then investigated with little finger and no retained secundines found. Uterus was the size of normal involuting uterus at this period and no pelvic exudate was felt.

Course in Hospital.—A moderate sized, firm, pelvic exudate developed in the right broad ligament in two days, and was palpable and tender in the right iliac fossa. Temperature fell in three days to about normal and after that ran an up and down course, patient having chills on second and third days. Patient left hospital, against advice, 26 days after admission, still having an irregular low temperature and slight pelvic exudate, but the mass palpable in the right iliac fossa had disappeared.

Note Three Months Later.—Patient has had no further symptoms since leaving the hospital and now feels entirely well.

Blood culture, January 19, 1911, 4 P. M., was negative.

Bacteriology of Culture from Uterus.—After 24 hours incubation, the culture tube showed no visible growth, but a dulling of the entire surface. Smears revealed practically a pure culture of a very minute, slender bacillus and a few cocci in chains. Subcultures on blood agar gave in 24 hours a profuse growth of minute, discrete dew drop colonies and three or four raised, opalescent colonies, 1 mm. in diameter. The former proved to be the minute bacillus and the latter the coccus. These two organisms were isolated with difficulty by streaking them on blood agar tubes, and the coccus demonstrated to be a streptococcus. Its pathogenicity was not determined. The small bacillus grew as above on blood agar only, and did not grow on bouillon, serum bouillon, plain, glucose, and plain serum- and glucose-serum-agar, litmus milk, potato, and gelatin. It was Gram negative, stained densely and best with carbol-fuchsin diluted in water, and was then seen as a very minute slender bacillus, showing a very polymorphic appearance, sometimes straight, sometimes comma-shaped, and varied from coccoid forms, some at the limit of visibility, to bacilli from 0.5 to 1.0 μ long. In all the subcultures this variation in form and size was noted. From the above data the diagnosis of *B. influenzæ* was made. This organism was sent as an unknown to Dr. George Baehr, of the Pathological Department of the Mount Sinai Hospital, New York City, and this same diagnosis arrived at by him.

The finding of the *B. influenzæ* in the case cannot definitely be explained, and to attribute it to the attack of influenza, 15 years previously, would certainly not be justifiable. But the similarity of this history to that of the only other recorded case is either to be considered as quite suggestive or else a rather unusual coincidence. The other possibilities to be considered are an accidental infection at the time of labor or else an infection of some portion of the patient's genital tract with a streptococcus and the *B. influenzæ,* previous to labor. This may have occurred from coitus with her husband who was suffering from the venereal infection, but the *B. influenzæ* in this latter condition is also uncommon. What part of the infectious process was due to the influenza bacillus and what to a streptococcus could not be determined, but from the predominance of the bacilli in the first culture tube, the surmise is justifiable that the *B. influenzæ* was also the main factor in causing the pelvic infection. It is interesting that the blood culture taken at the height of the temperature was negative.

The second part of this report concerns itself with a new blood agar medium for the cultivation of the *B. influenzæ,* but before proceeding with this it may be worth while to review briefly the history of blood media in relation to this organism.

* The isolation of the *B. influenzæ* is very difficult and was first performed by Pfeiffer. This he did by smearing agar tubes with pus from patients' bronchial secretions. From these cultures he was unable to secure growth in subinoculated plain agar tubes and realized that growth in the first cultures was due to some constituent in the pus. After trying many media he secured typical growth on an agar tube whose surface had been smeared with a drop of human blood removed aseptically. Next he undertook to find what constituent of blood was the necessary one. He found that the *B. influenzæ* would not grow on human blood serum but would grow on red cell agar made from washed red blood corpuscles. The final step was to discover what constituent of the red blood cells was the essential one. Accordingly he laked some washed red blood cells either by alternate freezing and thawing, or by addition of ether, which was later removed by evaporation in a vacuum. The stroma of the red blood corpuscles was removed by filtration through a "kieselgur" filter. The clear, chemically pure, blood coloring substance, dissolved in 0.6% saline solution was added in an amount of one drop to each tube of agar. These tubes were inoculated with the *B. influenzæ* and colonies appeared as numerous on them as on blood agar. Growth also occurred in hemoglobin bouillon, but not in tubes of agar mixed with stroma of red blood corpuscles from which all the hemoglobin had been removed.

Since this work other media for growing the *B. influenzæ* have been invented, but none are as satisfactory as blood agar.

Beck, a student of Pfeiffer, continued this work and found that blood agar made from pigeon's blood was the one most favorable for this organism's growth, it growing more slowly on human and rabbit blood agar. Nastjukoff reported growth of the *B. influenzæ* in pure culture on media of yolk of egg and claimed this was due to hematogen, which he isolated from it. Voges, after many experiments, was unable to verify this work of Nastjukoff. Capaldi also refutes this work because he found that the *B. influenzæ* grew very poorly on agar to which he added lecithin or hematogen. Cantani reported satisfactory growth on agar streaked with semen of animals, and claims that his work shows that the growth of the *B. influenzæ* cannot be attributed to hemoglobin alone, but is also due to cholesterin and serum albumin substances which occur naturally in semen. Kolle and Delius obtained good growth, especially on the bottom of the flask, when 0.25 to 0.5 cc. of pigeon's blood was added to 30 cc. of bouillon, this shaken, and then frozen and thawed to get the corpuscles laked and the hemoglobin in solution. Grassberger thinks that one gets better growth of the *B. influenzæ* in symbiosis with staphylococcus or on media on which staphylococcus was previously grown. Cantani found that the *B. diphtheriæ* and gonococcus promoted growth of the *B. influenzæ,* and Neisser grew it in symbiosis with the xerosis bacillus. Ghon and Preiss could not cultivate the *B. influenzæ* on hemoglobin free media, but obtained luxuriant growth on hemoglobin agar. Richter investigated the growth of the *B. influenzæ* on the following media with unsatisfactory results: sterile sputum, sterile bile, yolk of eggs, and agar with Schmiedeberg's ferratin.

* The following is extracted mainly from the article on Influenza by Beck, in Kolle and Wasserman's Handbook, Vol. III.

Huber invented and used successfully hematogen agar made as follows from Dr. Hommel's hematogen: Add caustic potash to a solution of hematogen in water till the reaction is strongly alkaline. Boil or steam, sterilize, and filter; the precipitate is separated from the filtrate which latter is a bright red fluid and can be sterilized in an Arnold steam sterilizer, without coagulation or injury. This sterile preparation is added to sterile liquid agar at 50°-60° C. and tubed. The hematogen must be sterilized separately because the original alkalinity must be preserved so that it will not coagulate when heated to 100° C. Huber reports that the growth is less luxuriant and slower on this medium than on blood agar, taking from 2 to 8 days to become visible, but the *B. influenzæ* seems to remain alive longer, he having made successful subcultures at the end of 35 days from a surface inoculated tube and at the end of 60 days from stab cultures. This work is important for it shows that oxyhemoglobin is not necessary for growth of the *B. influenzæ*, but merely the iron radicle of the hemoglobin.

One other medium is worthy of note: that of Bernstein and Epstein from the Pathological Laboratory of Mount Sinai Hospital, New York. This is made from whole beef blood and not from a definite blood or hemoglobin product. It is made as follows: "400 cc. of beef blood are drawn directly into a 500 cc. Erlenmeyer flask containing 30 cc. of a 1% solution of ammonium oxalate (to prevent clotting) and 0.5 cc. of formalin of 40 volume strength. The flask is shaken for two minutes. Thirty minutes are required for sterilization of the blood, which is then transferred in small quantities into sterile Erlenmeyer flasks and diluted with twice its volume of 0.9% sterile saline solution. This dilution reduces the actual formalin content to one part in 2400 of blood. This is allowed to stand for 24 to 48 hours for diffusion of formalin and then added to agar or bouillon in proportion of one part to fifteen. Luxuriant growths of pneumococcus, meningococcus, gonococcus and influenza bacillus are readily obtainable."

A résumé of these methods shows that the only media on which one can consistently and readily cultivate the *B. influenzæ* are those containing fresh blood, or hemoglobin obtained from fresh blood; for the slow growth on Huber's hematogen media cannot be considered satisfactory. The method used by Pfeiffer for obtaining hemoglobin is rendered complicated by the necessity of a freezing and thawing process or else by the necessity of evaporating the ether in a vacuum, procedures too cumbersome for use in routine manufacture of laboratory media. The method of Bernstein and Epstein is uncertain in yielding sterile media but when this is accomplished the media is very satisfactory. It is to be regarded with some skepticism if 30 minutes contact with formalin in a dilution of 1 to 860 is sufficient to sterilize the blood used. The recent work of Post and Nicoll, which the author working with Mr. Palmer has been able to confirm, would indicate that formalin is inefficient as a bactericide at this dilution, in this length of time.

Blood agar is usually made from blood obtained from a hospital patient. This is withdrawn with a syringe from the veins at the bend of the elbow and immediately mixed with agar in a flask and poured into sterile tubes. The inconvenience of this method and the difficulty of obtaining permission to get this blood, even when the laboratory is associated with a hospital is evident.

The two following methods were investigated in an attempt to provide a simple laboratory method for making a hemoglobin or blood medium capable of growing the *B. influenzæ*. Only the second one, however, proved successful.

The first investigation was an attempt to utilize a beautiful crystalline hemoglobin product, obtained from Armour and Company through the courtesy of their laboratory. A solution of this coagulated at 60° C., forming a muddy precipitate in a colorless fluid and was, therefore, impossible to sterilize when in solution. It was found that the material underwent no change when heated in a hot air oven at 115° C. for one hour, but this proceedure did not yield a sterile product for, although it was tried a number of times, in every case when dissolved in sterile distilled water and streaked on agar, in a 24-hour acrobic culture, a profuse growth of a large spore-forming bacillus occurred. This organism was not identified. A solution of unheated hemoglobin in distilled water was next freed from bacteria by passing it through a sterilized Reichel filter. This gave a solution, brownish red by transmitted light, which was added to tubes of melted agar at 45° C. in quantities sufficient to give a light brown medium, of about the same density of color as ordinary blood agar. There was always plenty of water of condensation present, and although many inoculations were made of a strain of the *B. influenzæ* and the strain isolated from the above patient, in no case was a visible growth observed, though usually in 24 to 48 hours many typical forms could be demonstrated in smears made from the surface of the inoculated tubes, and in a few cases successful plants were made from these tubes to blood agar tubes and tubes of the media made by the second method. This is not considered as evidence of growth on this hemoglobin agar, but rather a proof of just the opposite. Certainly this is not practicable as a laboratory medium.

Second method: Freshly drawn beef blood obtained from an abattoir was collected in a wide mouthed jar and defibrinated by shaking with a number of medium sized marbles. This was laked by adding an equal part of distilled water and rendered free from bacteria by passing through a sterile Reichel filter as above. This yielded a beautiful, clear, red fluid and 20 to 30 cc. of this were added to a liter of sterile melted agar at 45° C. and poured into sterile tubes. The medium which resulted was also perfectly clear, bright red and of the same density of color as ordinary blood agar. On this medium the two organisms, which were unsuccessfully tested on the hemoglobin agar, were successfully passed through 10 subcultures. The growth occurred in 24 hours, and was typical of the *B. influenzæ*, occurring luxuriantly in small, discrete, dewdrop colonies. Smears showed the typical morphology. Pneumococcus, streptococcus, streptococcus mucosus and gonococcus also grew luxuriantly.

This method is a modification of former methods, notably

that of Pfeiffer, and is believed to be the simplest yet devised for making blood agar. Its chief advantage over that of Pfeiffer is that the laking agent is one which does not interfere with growth of bacteria and does not have to be removed. From 40 to 50 cc. of this laked blood can be filtered in 24 hours through a Reichel filter of 50 cc. capacity. Where a larger quantity is needed a larger filter can be used. It is evident that the hemolytic qualities of an organism cannot be tested with this medium.

In conclusion the author wishes to express his indebtedness to Dr. H. T. Marshall for his helpful suggestions in this work, and also to Dr. George Bachr for the strain of the *B. influenzæ* used in this work and for his report on the organism which was isolated from the case reported.

The opportunity to study the above case was afforded the author by Dr. Makin, in whose service at the University of Virginia Hospital the patient was treated.

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HYPERLEUCOCYTOSIS OF HIGH GRADE IN BRONCHO-PNEUMONIA IN A CHILD.

By Charles R. Austrian, M. D.,

Assistant in Medicine, The Johns Hopkins University.

(*From the Medical Clinic of The Johns Hopkins Hospital.*)

On November 23, 1909, C. R., a colored child aged four years, was admitted to the Johns Hopkins Hospital, complaining of "cough and pain in the stomach and throat." The past history was negative, except for measles and chicken-pox one year ago. The illness which brought the patient for treatment began on November 9, fourteen days before admission, with cough—at first unproductive, occurring in nocturnal paroxysms, at times so severe as to induce vomiting, and later becoming more frequent with the expectoration of tenacious mucous sputum which was never blood-tinged. There had also been fever, night sweats, anorexia and constipation.

The child was small, fairly well nourished, with marked dyspnea and tachypnea, respirations fluttering, 100 to the minute. The alæ nasi were dilating, the lips cyanosed, and with each expiration there was a short grunt. The head was negative; there was no mastoid tenderness, nor signs of aural or meningeal disease. There was moderate general glandular enlargement.

The thorax was rounded; a rickety rosary was palpable; there was a tendency to "pigeon breast." The respiratory movements were mainly abdominal and the thoracic expansion was limited on the right side. The vocal fremitus was not tested. Percussion revealed Skodaic resonance at the right apex, tympany over the upper portion of the right lower lobe, and impaired resonance in the axilla, merging into dulness at the base behind. On the left side Skodaic resonance was present over the front as far as the third rib, though there was normal resonance below. Behind, dulness was present from the apex to the mid scapular region; there was slightly impaired resonance as far as the angle of the scapula, and normal resonance below. There was nowhere absolute flatness. On auscultation, intense tubular breathing was heard over both upper fronts and backs, also over the lower right back, and numerous consonating crackles were audible in the dull areas at the end of inspiration. Over the middle and upper part of the right lower lobe medium and coarse moist râles and a leathery friction rub were heard.

The cardiac dulness was not increased. There was marked

tachycardia with fœtal rhythm and the sounds were clear. Examination of the abdomen showed marked tympanites. The liver dulness extended from the sixth rib to a point 4 cm. below the costal margin in the right mammillary line, where a firm edge was readily palpable.

On November 24, there was a generalized clonic convulsion with unconsciousness, blepharospasm, turning of the head and conjugate deviation of the eyes to the left, and loss of sphincter control. After it had lasted fifteen minutes, the paroxysm was aborted by immersing the child in a hot mustard bath.

By November 27—the eighteenth day of the illness—the signs of consolidation at the apices had practically disappeared, but dulness, with tubular respiration and crepitation, was still present over the right lower axilla and back, and now for the first time a to-and-fro friction rub was audible over this area. The signs of consolidation were made out on the left side, from the apex to the angle of the scapula, and also over the lower front and axilla, where too there was a leathery rub. Two days later, the condition was more grave, and over the right mastoid, involving the tissues over an area about 5 cm. in circumference from its tip, there was a large ruptured bleb with brawny induration and tenderness about it, and the associated lymph glands were tender and swollen. The right tympanum was now tense, red, and lusterless. At 7 p. m. the child began to vomit and at 7.25 p. m. suddenly expired.

During the disease the temperature ran an irregular course around 103° F., showing marked remissions after the sponges, the fever occasionally falling as much as 3°F. in two hours. Polypnea was marked and persistent, the respiratory rate varying from 60 to 106 to the minute. Tachycardia was also pronounced, the pulse ranging from 140 to 195 to the minute.

This clinical picture is common—a case of pneumonia with one of its most usual complications, mastoiditis—but the blood findings make the case of interest.

On admission, the red blood cells numbered 4,860,000 per cmm., the hæmoglobin was 87 per cent (Sahli) and the leucocytes 130,000 per cmm. Seven hours later, the leucocytes were 144,000 per cmm.; on the morning of November 24, they had increased to 183,000 per cmm. and that evening reached a maximum of 206,000 per cmm. During the following four days they varied between 126,000 and 156,000, but with the onset of the mastoiditis again rose to 192,000 per cmm.

The marked leucocytosis caused us to suspect the presence of a purulent focus, or the possibility of a leucemia with a terminal pneumonia. The former we had no reason to assume, inasmuch as there were no signs of pus anywhere, no evidence of an empyema, of a sinus infection, of otitis or of mastoiditis, the latter not appearing until the day of death. A possible leucemia was excluded by the differential counts:

Ehrlich Stain.—The red corpuscles showed very little polychromatophilia, no marked anisocytosis or poikilocytosis, few normoblasts and no megaloblasts. The white cells, in general, were readily classified, one type, however, being difficult to identify, *i. e.*, a rather large cell with pale homogeneous, pink-staining, non-granular cytoplasm, and a slightly lobulated nucleus with a well defined chromatin net and sharply defined nuclear membrane.

In 500 cells counted there were:

	Nov. 24. Cells.	%	Nov. 26. Cells.	%	Nov. 28. Cells.	%	Nov. 29. Cells.	%
Polymorphonuclear neutrophiles	260	52	280	56	300	60	270	54
Polymorphonuclear eosinophiles	20	4	15	3	10	2	15	3
Lymphocytes	120	24	105	21	100	20	110	22
Large mononuclears	3	0.6	8	1.6	10	2	20	4
Transitionals	15	3	10	2	5	1	10	2
Myelocytes	60	12	70	14.0	50	10	60	12
Unclassified	22	4.4	12	2.4	25	5	15	3
	500	100.0	500	100.0	500	100	500	100

In 500 white cells counted there were:

Normoblasts	4	6	2	9
Megaloblasts	—	—	—	—

The relative lymphocytosis is not unusual during an acute infection in a child of four, and the presence of 12 per cent of myelocytes does not necessarily militate against a diagnosis of leucocytosis as differentiated from leucemia (Cabot, Musser and Steven). Moreover, the absence of a marked anæmia and the post mortem findings exclude a leucemic process.

The post mortem findings were as follows (Dr. Winternitz):

Anatomical Diagnosis.—Broncho-pneumonia, bilateral. General lymphoid hyperplasia and hyperplasia of the bone marrow. Acute mastoiditis, right, with thrombosis of the superior petrosal sinus and of the adjacent sinuses of the brain. Congestion of the brain, especially of the right hemisphere. Cloudy swelling of the liver and of the kidneys.

The body is that of a fairly well nourished child 93 cm. in length. Rigor mortis is present. Over the right mastoid there is swelling with reddening of the skin, the upper layers of which are broken.

The peritoneal cavity is normal except for a great enlargement of the mesenteric lymph glands, which, on section, have a gelatinous, homogeneous appearance.

The left pleural cavity contains a slight excess of straw-colored fluid; the right is partially occluded by recent fibrinous adhesions.

The thymus is small and pinkish brown in color.

The heart is not enlarged; the myocardium and the valves are normal.

Lungs: the left lung is pale, voluminous, and retains its shape after removal. It is everywhere crepitant except over a few small areas of consolidation in the posterior portion of the lower lobe. The bronchi contain an excess of fluid, and the bronchial lymph glands are much enlarged. Right lung: the pleural surface is covered with a friable grayish exudate which is several millimeters in thickness. Two-thirds of the lower lobe is occupied by areas of consolidation which, on section, are dry, granular, and slightly translucent, and there are a few small areas of like character in the upper lobe.

The spleen measures 9 x 4 x 2 cm. and retains its shape after removal. Its capsule is delicate and the red splenic pulp is seen through it. On section, the Malpighian corpuscles are gray and tremendously enlarged; so much so, that neighboring

oncs are almost in contact. Neither the fibrous tissue nor the pulp is much increased.

The stomach, the duodenum, the pancreas, and the intestines are normal. There is no hyperplasia of Peyer's patches or of the solitary follicles.

The liver measures 19 x 12.5 x 5 cm. The capsule is thin and delicate. The liver parenchyma is purple in color, and on section the lobules are large and distinct. The gall bladder is normal.

The brain: the dura mater is thick and adherent. The right cerebral hemisphere is covered with dilated vessels; the left is pale and only a few of the vessels are injected. The superior and inferior petrosal sinuses on the right are distended and filled with thrombi. There is a large amount of pus in the spongy portion of the bones of the right middle ear, and the ossicles lie free in a necrotic sequestrum. The brain tissue is normal except for the congestion of the right hemisphere.

Microscopic Examination.—Lungs: the pleura is covered by an exudate consisting mainly of polymorphonuclear leucocytes. The alveoli of the lungs are filled with an exudate varying from a very cellular material in which mononuclear cells predominate, to one almost purely fibrinous in character, and where the latter type is present the alveolar walls are involved. In places there are zones of coagulation necrosis.

The thymus shows well preserved gland tissues with conspicuous Hassal's corpuscles.

Sections of several lymph glands show a marked dilatation of the sinuses, in which there are many large mononuclear cells with pink-staining cytoplasm and vesicular nuclei. A few of these cells show definite granular inclusions. The lymphatic strands are coarse and show an increase of the mononuclear elements. The centers of the lymph follicles stain deeply and uniformly with eosin.

In the anterior and middle portions of the hypophysis are cyst-like areas which contain colloid in excess, and in one of these areas there is a fibrous thickening in which there are a few typical mucous glands.

The liver cells are swollen and there is an infiltration of the parenchyma with mononuclear cells, some of which have deep pyknotic nuclei. Polymorphonuclear leucocytes are less numerous, and only an occasional myelocyte is seen. The stellate cells of Kupfer are enlarged, and in some places have taken on phagocytic activity. The predominating cell in the blood clots is the large mononuclear lymphocyte.

The bone marrow shows marked hyperplasia, but there are still some areas of fat remaining. In the smears and sections the large neutrophilic myelocyte is the predominant cell. The erythroblastic tissue is increased somewhat less than the myeloblastic and relatively few normoblasts and megaloblasts are seen. The polymorphonuclear neutrophiles are relativcly few and there are many giant cells. With Ehrlich's stain only a few myeloblasts are seen. In the marrow there are several small areas of hæmorrhage, and near the areas of softening a few small thrombi are found.

Hyperleucocytosis in the sense of excessive leucocytosis is not uncommon and counts of 80,000 or more leucocytes per cmm. have been reported in many conditions. Leucocythemias of over 100,000, except in leucemia, however, are comparatively rare. The following may be cited as the maximum counts found in a cursory survey of the literature on this subject:

Limbeck,[1] quoted by Sisto,[2] noted a leucocytosis of 120,000 in a patient with multiple carcinoma, and Kast reported an identical count in a similar condition.

Hirschfeld and Kothe[3] report a leucocytosis of 190,000 (56 per cent polymorphonuclears and 7 per cent myelocytes) in a case of appendicitis gangrenosa complicated by a hæmorrhage from a duodenal ulcer. This is a most phenomenal finding, as may be seen from the exhaustive study of Busse.[4]

Felsenthal[5] counted 148,229 leucocytes per cmm. in a child with gangrenous diphtheria and petechiæ.

Osler[6] cites a case of lobar pneumonia with 114,000 white cells, and Læhr, quoted by Emerson,[7] Arneth and Türk,[8] found 115,000 leucocytes per cmm. in a similar case, and these authors could find no more marked leucocytosis in pneumonia reported in the literature as late as 1904. Cabot[9] mentions a case of broncho-pneumonia complicating pertussis, in a girl aged six years, where the leucocytes reached 94,600 per cmm. and another case where they were 185,000 per cmm.

The most marked leucocytosis in pneumonia in the records of the Johns Hopkins Hospital is 105,000 per cmm. in a man aged 25 years.

Fletcher and Sappington[10] reported a case of splcno-hepatic cirrhosis in which there was a leucocytosis of 136,000 per cmm. (89 per cent polymorphonuclears) and this is cited by Cabot[11] as the most marked polymorphonuclear leucocytosis he could find on record.

Those who have reviewed the literature on leucocytosis seem to have overlooked an article by Steven[12] on broncho-pneumonia in childhood, in which a case is reported with a leucocyte count of 236,000 per cmm. (33.6 per cent polymorphonuclear, 50.2 per cent lymphocytes, 15.2 per cent large mononuclears, 0.57 per cent eosinophiles). This case, it is seen, is practically identical with the one here described, *i. e.*, a child twenty-two months old, with cyanosis, dyspnea, tachypnea (103 to minute), crepitant râles over both lungs, and convulsions.

To sum up, we have here a phenomenal hyperleucocytosis occurring in a case of broncho-pneumonia in childhood.

The formula as determined by repeated differential counts shows a marked mononucleosis and a moderate myelocytosis—a picture neither uncommon nor unique in this disease.

Leucemia is definitely excluded by the history, by the physical findings and by the necropsy.

The case seems worth recording, as this hyperleucocytosis is second only to that reported by Steven in a similar case.

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THE VIABILITY OF PARASITIC OVA IN TWO PER CENT FORMALIN, WITH ESPECIAL REFERENCE TO ASCARIS LUMBRICOIDES.

By ROGER S. MORRIS, M. D.
Associate in Medicine, The Johns Hopkins University.

(From the Clinical Laboratory of The Johns Hopkins Hospital.)

It has been a routine procedure for several years in the clinical laboratory to preserve stools, for purposes of demonstration, with formaldehyde. The fæcal material is finely comminuted in water so that a relatively thin suspension is secured. Commercial forty per cent formalin is then added to the fæcal suspension in such quantity that the resulting mixture contains the reagent in a strength of two per cent. For most purposes stools are well preserved in this way and when tightly stoppered in bottles, may be kept for an almost indefinite period. Putrefaction and fermentative changes are inhibited successfully.

The chief purpose for which we have employed formalin has been the preservation of material containing parasitic ova. Eggs of the commoner cestodes of man—Tænia saginata, Hymenolepis nana, and Dibothriocephalus latus, have retained their morphology fairly well, though the thin-shelled ova of the last two have shown greater alteration than those of Tænia saginata. To all appearances, the eggs have been killed, as no evidence of further development has been observed.

Trematode material has been more scanty, as we have only had specimens of Schistosoma hæmatobium and Schistosoma japonicum. The former has shown less change in shape, and in both specimens the eggs appear to have been killed.

With nematode ova, there have been rather interesting results. The eggs of the hook worm, Ankylostoma duodenale and Necator americanus, exhibit a certain amount of distortion of the shell. The formalin apparently does not kill the ova at once. Fæces containing eggs in the two-, four-, and eight-cell stages have been found later to have ova which in the majority of instances have passed beyond this stage, though death must be reasonably prompt, as we have never found embryos within the shell or free in the fæces. Inasmuch as the same stool has been examined by eighty to ninety or more students simultaneously, some of whom have studied several preparations, it seems probable that embryos would have been observed, if present. Eggs of Trichuris trichiura and of Oxyuris vermicularis have presented no signs of development in fæcal suspensions containing two per cent formalin.

Findings of special interest have been met with in connection with the ova of Ascaris lumbricoides. In January of 1909, while demonstrating a stool containing the eggs of Ascaris lumbricoides to the class, it was noted that many of the ova contained embryos which frequently exhibited active motility within the shell. The stool was of unknown source, unlabeled, and had been on a shelf exposed to the light but not to the direct rays of the sun for an unknown length of time. It had probably been preserved with formalin (odor). The same specimen was demonstrated to classes in June, 1909, January and June, 1910, and again in January, 1911, and on each occasion actively motile embryos were observed within the shell. In fact, they were so numerous that there was practically no difficulty in demonstrating them in every preparation examined. Embryos which were well preserved but non-motile during the short period of inspection were much more abundant than those seen in a state of active motility. Often an ovum containing a living embryo had lost the albuminous envelope. A few embryos which had escaped from the shell were observed but in all instances they were dead. An examination of the stool on May 19, 1911, demonstrates that living embryos still persist, *i. e.*, about twenty-nine months after they were first observed in the specimen. How much longer they have been there it is impossible to say.

An opportunity to confirm the results just narrated presented itself some time ago. O. R., Surgical No. 25086, white, æt. 13, was admitted to the surgical service of Professor Halsted on December 4, 1909, on account of double cataract. The routine fæcal examination disclosed the presence of "many Ascaris lumbricoides ova in the stool." The eosinophiles amounted to seven per cent. On December 9, 1909, a specimen of fæces was suspended in water and formalin was added so that it was present in a strength of two per cent. Microscopic examination at that time showed an enormous number of ova of Ascaris lumbricoides, both fertilized and unfertilized, the former predominating. The stool was demonstrated to the class in January and June, 1910. The ova were well preserved and no suggestion of

embryo formation was noticed, although carefully looked for. January, 1911, the specimen was used again for class demonstration and at this time a few fertilized ova were found which contained embryos, some of them actively motile. On May 19, 1911, examination of the specimen shows an *apparent* increase in the number of eggs which possess embryos, and in the first preparation studied an active parasite was seen. All seem to be well preserved morphologically and in the more mature embryos it is probable that prolonged inspection would reveal definite signs of life. Since the specimen was first obtained, it has been kept in a brown glass bottle, securely corked, on a shelf in the laboratory where it has been constantly exposed to the light but, like the preceding specimen, protected from the direct rays of the sun. It is unfortunate that examinations have not been made at more frequent intervals to determine how soon the living embryos first appear. They probably developed sometime between the sixth and thirteenth month.

That the ova of Ascaris lumbricoides are extremely tenacious of life has long been known. Davaine[1] showed that the eggs may be viable and still exhibit no sign of development for a considerable period of time. From the fæces of an infected child he recovered the eggs of Ascaris lumbricoides by washing the dejecta. They were then transferred to water on October 8th. The material was examined from time to time and it was not until the following April 14 that signs of development were noted. Three weeks later the embryos were seen in the shell. Later Davaine[2] showed that the embryos may remain alive in the shell for three years. Stiles and Gardner[3] have recently demonstrated that ascaris eggs are quite resistant to decomposition. In fæcal matter kept for four months (117 to 121 days), about eighty per cent of the ova appeared to be dead. Leuckart[4] proved that the ova can withstand desiccation, which, however, arrests the embryogenic process.

Thus, it is evident that the viability of Ascaris lumbricoides ova is not easily destroyed under the conditions usually met with in nature. It might therefore be supposed that the eggs would prove less susceptible to antiseptics than those of the other common intestinal parasites of man. With formaldehyde, at least, this is the case. An incomplete review of the literature on Ascaris lumbricoides has failed to reveal similar observations.

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ANTERIOR POLIOMYELITIS—NOTE.

I

The Rockefeller Institute for Medical Research, of New York City, announces that it will devote its resources very largely during the present season to the study of anterior poliomyelitis (infantile paralysis) and to the treatment of acute cases of this disease in its hospital. Physicians and health officers desiring to co-operate in this investigation may do so by sending information concerning the occurrence and prevalence of this disease, or by referring acute cases to the Hospital of the Rockefeller Institute. Dr. Flexner renews his request of last year that whenever possible a portion of the spinal cord and of the naso-pharyngeal mucosa derived from fatal cases of the disease be sent to him. Specimens should be preserved in glycerin and sent by mail to Simon Flexner, M. D., 66th Street and Avenue A, New York City.

II

Anterior poliomyelitis * is, so far as known, a communicable disease, being communicated from one patient to another and also by means of a third person. It occurs in epidemics and tends to spread along the lines of greatest travel. There is reason to believe that it is prevented from spreading by quarantine, and with the very great prevalence of the disease in the summer of 1910 it is the opinion of this committee that it is essential that it should be made a reportable disease in all States in order that its presence may be detected and its spread guarded against.

Of particular significance are the so-called abortive cases, where indefinite ailments occur in children in communities where frank paralysis also exists. These abortive cases of infantile paralysis are undoubtedly a source of infection, and their record and study is of much importance. In a community where cases of infantile paralysis occur, cases of illness with sudden onset of fever and meningeal symptoms should be closely watched and regarded as possibly infectious. In such cases even recovery without paralysis does not establish the fact, that the case was not abortive infantile paralysis.

All cases of infantile paralysis should be strictly quarantined, sputum, urine and feces being disinfected, and the same rigid precautions being adopted as in scarlet fever. This quarantine should, in the opinion of the committee, last for four weeks in the absence of definite knowledge as to when the infection ends. Children from infected families should not be allowed to go to school until the quarantine is abandoned. The transportation or transfer of acute cases in public conveyances should be strictly forbidden. It would be very desirable to adopt provisional quarantine measures in suspicious cases in a community where an epidemic prevails. The report of all cases of infantile paralysis to the public health authorities should be enforced by law, and all deaths from this cause should be properly described and registered. A careful study of epidemics by public health authorities is strongly advised.

(Signed) Robert W. Lovett, M. D., *Chairman.*
Henry Koplik, M. D.,
H. Winnett Orr, M. D.,
Irving M. Snow, M. D., *Secretary.*

* Circular issued by the American Orthopedic Association and the American Pediatric Society in reference to acute epidemic poliomyelitis, and addressed to health authorities and boards of health.

THE STARNOOK—A NEW DEVICE FOR THE REST-CURE IN THE OPEN AIR AND FOR OUTDOOR SLEEPING.*

By S. Adolphus Knopf, M. D.,

Professor of Phthisiotherapy at the New York Post-Graduate Medical School and Hospital.

Every physician interested in the treatment of tuberculosis knows how difficult it is to have anything in the line of additional porches or verandas built onto a city home. First of all in cities, like New York for example, wooden constructions are not permitted. The vast majority of houses are tenement or apartment houses, and even if there should be space, the owner would not permit any addition.

My purpose to-day is to show to those who are so fortunate as to have their own house in city or town, or to have an accommodating landlord, how they may avail themselves of a very new and practical device which will answer all purposes for outdoor life by day and by night. I am indebted to Mr. H. C. Ford, a young mechanical engineer, and to the Starnook Company, with which he is associated, for the con-

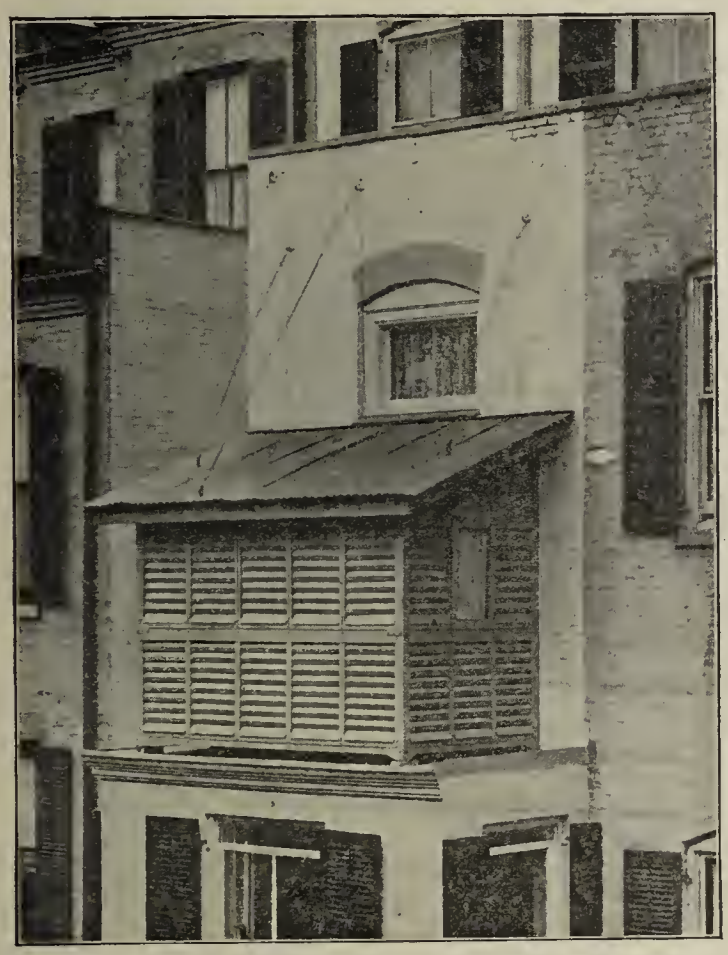

Fig. 1.—Starnook (Knopf Model) for the rest-cure in the open air and for outdoor sleeping at night.

struction of this device. As I have said, it is suitable for the rest-cure in the open air by day and for outdoor sleeping by night, and as the thought of the latter use came first, it has been called the "Starnook." This name is very appropriate for, as will be seen from the following description, on a clear night the stars can be seen from this little nook.

I have slept in my starnook since October, 1910, and never have I had more peaceful nights, more sound and more refreshing sleep. To lie outstretched in the warm bed, breathing constantly the pure, fresh air, to be able to gaze at the beautiful sky, and watch the starry constellations without any effort, is a sensation which must be felt, for it cannot be described. I am inclined to believe that the most restless and nervous person will soon fall asleep in a quiet starnook. On bright, moonlight nights the scene is equally enchanting. Even on rainy nights with roof overhead and the slats of the shutters open to admit air, the sensation is a cozy one. One

Fig. 2.—Interior of Starnook (Knopf Model) with windows, roof, and shutters closed. View from adjoining bathroom.

soon gets accustomed to the rain trickling on the roof and the monotonous noise of it is sleep inviting.

My purpose in having this starnook constructed was that it might serve as a model for tuberculous, pneumonic, or nervous patients who have been directed to live and sleep in the open air. As will be seen my own starnook (Fig. 1) is built on an extension at the rear of the house, but it could also rest on posts or columns, or triangular supports attached to the walls. The starnook consists of three walls composed of frames holding movable slats, of a roof and a floor. It is all made of galvanized iron with the exception of the floor, the

* Abstract from a lecture on Aerotherapy, delivered at the Johns Hopkins Medical School, Baltimore, March 27, 1911.

window sash and the roof-frame. The wall of the house closes the fourth side through which access is had to the starnook by a long window or a door. It is about 9 feet long, 6 feet deep, 6 feet high at the outer side, and 8 feet next to the house. It can also be made 8 feet deep and will then hold a bed and couch or two beds.

In either end is a glass window which can be opened outward, and Florentine glass fills the triangular spaces at each end under the slope of the roof, which rests a short distance above the walls to allow for free circulation of air at all times.

Figure 1 shows the starnook in use at night in rainy or stormy weather. Figure 2 gives an interior view, all closed except the door leading from the house into the starnook. On a clear night when there is no fear of rain or snow the roof of the starnook is raised by means of a crank and counterweights.

As seen in Figs. 3 and 4, the roof can be completely raised against the wall of the house and an unobscured view of the

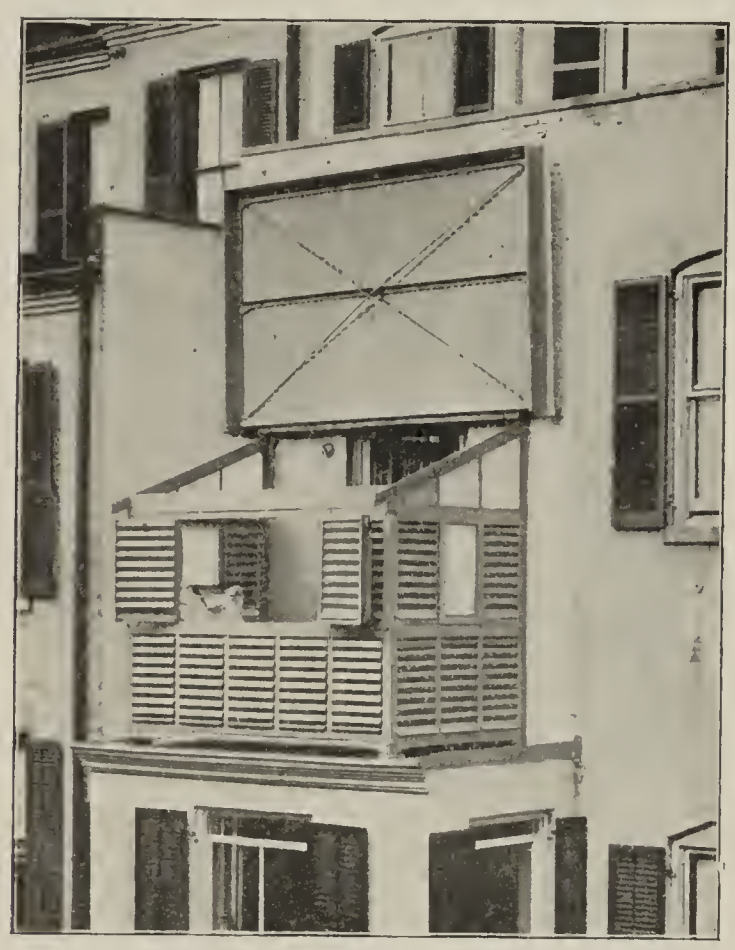

Fig. 3.—Starnook (Knopf Model) transformed from night-shelter to a pleasant rest-cure porch by day.

sky can be had by the occupant of the bed. During the day the starnook can be transformed into a typical rest-cure veranda. Three upper sections of the front shutters can be entirely opened, and with the two windows open and the roof up one is certainly out of doors. Figure 3 shows the starnook transformed from a night shelter to a pleasant resting porch by day time.

Figure 4 gives an idea of the interior aspect of the starnook by day with roof and all windows open.

The advantages of this device are manifold. When painted to match the house it forms an attractive addition. The slats that form the walls, instead of being straight, are bent inward at the lower edge and outward at the upper in such a way that when partly open they permit a free access of air, yet neither the bed nor the occupant of the bed can be seen by neighbors and absolute privacy is thus secured (Fig. 5).

In very stormy weather the shutters can be tightly closed (Fig. 6) to protect the occupant from rain, drifting snow and strong winds, and still there will be enough open spaces to allow the freest circulation of air. The lower sections of the shutters are manipulated simultaneously by means of a handle conveniently located so as to be reached from the bed. Each upper section has an individual handle whereby the slats can be placed at any angle desired. The handles are of wood so as not to chill the patient or occupant when he touches them in cold weather. An electric light which can be turned

Fig. 4.—Interior of Starnook (Knopf Model) with windows, roof, and shutters open. View from adjoining bathroom.

on and off with the aid of cords by the occupant of the bed, and a push button to call a maid or nurse in case of illness, complete the arrangement for comfort.

Sometimes the starnook cannot be constructed so that the roof can be raised upward to rest against the wall of the house. If this is the case, then the roof has to be tilted outward. When for one reason or other it is desirable to have the construction on the roof of the house, a starnook can be constructed with a little shack, the two joined together so that the latter can be heated when serving as a dressing room. To make a good support for the roof of the starnook when raised, the shack would have to be somewhat higher. Another way is to divide the roof into two sections so that they may better

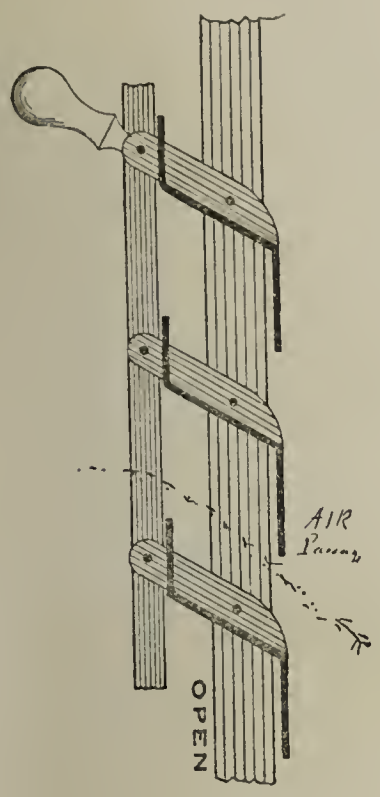

Fig. 5.

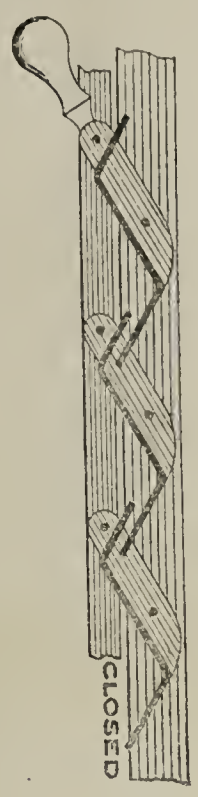

Fig. 6.

Fig. 5.—Diagram showing the mechanism of the movable iron slats.—Open.

Fig. 6.—Diagram showing the mechanism of the movable iron slats.—Closed.

withstand stroug winds when the roof is open. The same plan can, of course, also be carried out on the ground, in the yard, or garden. If it is desired to have a double starnook, the two devices can be joined, the bathroom and dressing room being between them.

To the timid who are afraid of sudden rain showers or snow storms and believe that they cannot get the roof down quickly enough, or who fear to get out of the warm bed for the purpose of lowering the roof, there can be arranged an electric motor manipulating the raising and lowering of the roof quickly and securely, operated by means of a push button within easy reach from the bed.

It is hoped that with a demand for a number of starnooks, two different standard sizes can be put on the market at very reasonable prices. In presenting this new device to the profession and the public, the inventors trust to have been in a measure helpful not only in solving the problem of outdoor sleeping and outdoor resting for the tuberculous in cities, but also to have given opportunity to other sufferers to recuperate, and to the well and strong to enjoy constant fresh air, at least at night, and enable them to be more frequently in touch with nature than is granted to most city dwellers.

THE HAVEN OF HEALTH.*

A REVIEW.

By W. H. Bergtold, M. D., Denver, Colo.

In these days of wood-pulp paper and cheap bindings, it is refreshing to see and to possess a book which is venerable with age, so old that it is, as it were, a voice from the ancient dead. There is now such a book before us, and it will be used as a text for my portion of this evening's talks.

Let us read its title page, a photograph of which is here presented for your inspection (see p. 304); printed in 1636, the book harks back 274 years, and since it was written (1584) eleven generations have been born, have run the gamut of human efforts, hopes, desires, and sorrows, and have died. It seems a long time to me. Is it not of striking interest to us at this precise time and in this State, to see by the title page that nearly three hundred years ago a woman could run a printing establishment?

As a material object the volume has the additional attraction of exhibiting signs of the ravages of real book-worms.

How many of our present books will be found, 274 years from this day, in as good a condition as this old book? Very few, it is safe to predict.

The preface to this Haven of Health is inscribed 1584; such a date means but little to me unless I can orient myself by other chronologic marks. Perhaps some of you may have the same feeling, which will be excuse sufficient for me to try to fix this period in our minds by showing its relation to other dates and things. Elizabeth (1533-1603) was reigning in England when Coghan was writing, and he specifically mentions her on page 159.

Shakespeare's span was from 1564 to 1616; this shows us that the great dramatist was a young man of but twenty when Dr. Coghan's dedicatory preface was finished. If we think of medical men of the immediately preceding, contemporaneous, and directly succeeding years, we realize that but a little while had elapsed since Servetus was burned at the stake, that Paracelsus had been dead less than fifty years, and that Van Helmont was but a child of seven at the issuance of the first edition. Only two years before, Galileo had discovered the principle of the pendulum, and before he had made his immortal discoveries of Jupiter's moons, this book had gone through at least two editions. Some renowned medical men were born about this time; Harvey six years after the book was written, and Willis and Sydenham shortly before it came out in the fourth edition.

When the book was chosen as a subject for to-night's paper, the speaker immediately wrote to the secretary of the Royal College of Physicians, England, for information concerning Coghan; here is the result of this correspondence:

Royal College of Physicians,
Pall Mall East. London, S. W., May 11, 1910.

Dear Sir:—

I send you herewith some particulars of Thomas Coghan, M. A., which have been gleaned from various sources, and have, so far as is possible, been verified. . . . .

Yours faithfully,
(Signed) W. Fleming.

W. H. Bergtold, Esq., M. D.

* Read before the Denver Medical History Club, January 6, 1911.

"Thomas Cogan, 1545-1607, physician, was born about 1545 at Chard, Somersetshire. He was educated at Oxford, graduated B. A., January 14, 1562-1563, M. A., July 5, 1566, and M. B., 1574. He became a Fellow of Oriel College in 1563, continuing until 1574. In 1574 he resigned his Fellowship and then (or in 1575) was appointed Master of the Manchester grammar school. He practiced as a physician at Manchester, taking a degree in that faculty in 1574. Before 1586 he married Ellen, daughter of Sir Edmund Trafford, and widow of Thomas Willott, who had property in Manchester. In 1591-3 he was the family physician of Sir Richard Shuttleworth. In 1595 he presented Galen's works, and other medical books, to the library of Oriel, where they are still preserved. He resigned the schoolmastership before 1602, died in June, 1607, and was buried on the 10th of that month in the Church of St. Anne's at Manchester. His will mentions property both in Somersetshire and in Manchester, and bequeaths books to all the Fellows and other officers of the college, and 4th, to each boy in the school. His widow died in 1611.

His works are:

1. The Well of Wisdome, containing Chiefe and Chosen Sayings Gathered out of the Five bookes of the Olde Testament . . . . 1577.

2. The Haven of Health, made for the Comfort of Students . . . 1584. (Several later editions.) With this was published "A Preservation from the Pestilence, with a short censure of the late sickness at Oxford," and several books in Latin intended as text-books.

THE

HAVEN

John of Hohlo 1726

HEALTH.

Chiefely gathered for the comfort of Students, and conſequently of all thoſe that have a care of their health, amplified upon five words of *Hippocrates*, written *Epid. 6. Labor, Cibus, Potio, Somnus, Venus.*

Hereunto is added a preſervation from the Peſtilence, With a ſhort cenſure of the late ſicknes at Oxford.

By THOMAS COGHAN Maſter of Arts, and Batcheler of Phyſicke.

Eccleſiaſticus Cap. 37.30.

By ſurfeit have many periſhed: but he that dieteth himſelfe prolongeth his life.

The fourth Edition, corrected and amended.

LONDON,
Printed by ANNE GRIFFIN, for ROGER BALL, and are to be ſold at his, ſhop without *Temple-barre*, at the Golden Anchor next the Nags-head Taverne. 1636.

Wood, in his "Athenae Oxoniensis," from which most of the above notice has been taken by the writer of the article in the "Dictionary of National Biography," finishes with:

What other things he wrote I know not, nor anything else of him, only that he deceased at Manchester, in sixteen hundred and seven, and was buried in the Church there 10 June leaving behind him the character of an able physician, and Latinist, a good neighbor, and an honest man.

Through this information it becomes evident that Dr. Coghan was a man of parts, estimated by the then existing standards; one notes, too, with surprise that he did not get his degree in medicine until he was 29 years old, which may be of some comfort to those who regret that a son is, in these days, so long in going through the academic and professional schools. It does no violence to historical evidence to assume that the practice of medicine in those days was just as keen a competitive game as it is now, and Coghan's taking up teaching with practicing lends support to this notion. You will note that his biographer describes him as an "able physician"; there is however, to me, an indefinable something in this book, which gives me the impression that this man was not so much a real clinician as a student of medicine, a man who doubtless saw something of actual practice, but who wrote more from his book knowledge than from his bedside experience. This feeling has come to me between the lines of his book, as it were, notwithstanding that he clearly indicates that his book is intended as a guide to the preservation of health only, and the feeling may be wholly unwarranted.

Years ago in studying the birds mentioned by Shakespeare, the speaker gleaned a passing insight of the conditions of life in England during the period covered by the editions of this book; while the savagery of the times has doubtless been overdrawn, yet, softening it all we can, life then and there was far from gentle, and medicine was on a similar plane. We are apt to forget that there were no carpets, that dishes and forks were all but unknown at the table, and that slices of bread, called "trenchers," were served, to be used in place of plates. One gathers an inkling of these conditions, it seems to me, from various things in this book of "Health."

There was no such thing as sanitation, or hygiene; William Shakespeare, the poet's father, was fined, in 1552, twelve pence for not removing household dirt and refuse from his own door.

If one reads this book carefully and tries, even in a cursory way only, to follow some parallel and radiating lines of study suggested by it, one gains, it might be said, a liberal education. Let me hint at some things which aroused keen interest as the book was perused.

It is probably fair to assume that Coghan was as well educated as any average college man of his time; in effect it may be correct to feel that he was likely to have been better schooled than the majority of his classmates, since we find him teaching, and later, head master of a considerable school at Manchester. It is highly probable, then, that his pages reflect, tolerably well, contemporaneous knowledge, general and special. Hence one notes with interest the extremely divergent spelling in different parts of the book; it might be taken to signify that English spelling had not yet crystallized.

One sees, too, the use of "V" where to-day "U" is used, and also two "V's" for "W," that is to say, "double U." This bizarre spelling was considered by some in those days, it is said, to be "smart."

One stumbles in reading a word like "rise" for rice, "rere" for rare, "limmes" for limbs, "todes" for toads, and to a botanist "cinckfoile" seems indeed odd. The obsolete words look strange; "eftsoons" for soon is one. "Gisar of foule," while rather foreign in looks, becomes, after a little study, "gizzard of fowl." We meet with many words which look as though one ought to use them now; "misorder" in the following is one: "Wherefor it is better to preserve health by sobriety and temperance, than by surfit and *misorder.*" "Discommodities" for inconveniences and "dispraised" for discountenanced are two other examples. The modern verb "let" and its parts sound queer when used as a synonym for "hinder." Frequently one finds, in a single sentence, obsolete and living words of to-day, the latter however in a strange sense. Thus, in speaking of butter he writes: "Wherefore it is good for such as be commonly costive; and this experience I have of it, that some .... which eat no bread but *manchet,* by the eating of browne bread and butter in the morning fasting, (which is a Country mans breakfast), have beene made as *soluable* as if they had taken some purgation."

Vinegar made from ale is "aliger," while cider made from pears is "piery." "Oppilation" for constipation warns us that we would have to learn a new vocabulary if we were to converse with, and understand, our sixteenth-century *confrère,* on the value of cheese as a food.

We all know, through our reading along the lines of ethnology, that many living barbarous people consider the entrails of animals a great delicacy; the North American Indian has been described many times as eating the still warm small intestine of a freshly killed buffalo, deer, or steer, devouring it raw by the yard, as it were, deftly milking out its contents as a mere incident in the swallowing of the tid-bit. Coghan gives a hint of the survival in England, at least in a modified form, of a similar habit, when he discusses the uses of the inwards of beasts as food, calling the small intestine "chitterlings."

With us to-day there still remains some trace of this custom, for we still eat sausage, do we not?

The most interesting parts of his strange vocabulary are the words which seem surface indications of the distinct, but then coalescing, linguistic streams, the Anglo-Saxon and the Norman, which have since flowed down the channel of time, merging as the English of to-day. Such indications are, for example, "milt" for spleen, "reines" or "reynes" for kidneys; "mo" and "moe" for more are true middle English words which make us think of the negro pronunciation of more. The possessive is formed in three ways, "Noah, his floud," Noah's floud," and the "floud of Noah." While we have delved very briefly into this fascinating side issue, even this little takes us back to the plastic and formative period of our tongue, making us realize anew that the way has been long to this our day of condensed, yet amplified and exact, English. In addition to these indications of age, there are the words about America in the foreword "To the Reader" which are even more striking, to wit: "Whereas now through the providence of God, and the travaile of men, there is found further in the West, as it were a new world, a goodly countrey named *America,* or new India, for largeness, plenty, wholesome and temperate ayer, comparable with Affrike, Europe or Asia."

This old volume gives many examples which go to prove anew the truth that "history repeats itself"; the following quotation, with a little alteration, might well be taken for the warning recently ascribed to one of our captains of finance:

> And what commodity a good warraine of Conies bringeth toward the keeping of a good house, men of honour and worship that love hospitality doe well know. Which vertue being acceptable to God, and a singular benefit of all the country round about them (the more it is to bee lamented) is every day more and more neglected in England. The chiefe cause thereof (as wise men think) is wastefull and sumptuous apparell, now commonly used in every degree farre otherwise than *William Rufus* did, who being a kings sonne and the second king of this land after the conquest, was thought to exceed, when he bestowed a marke upon a paire of hose, using commonly to bestow but three shillings.

Likewise a loud complaint of this day had its counterpart three hundred years ago, a fact plainly seen when we read in the preface to the use of fish, remarks as follows: "This much of flesh. Now concerning fish which is no small part of our sustenance in this Realme of England. And that flesh might be more plentifull and better cheap, two days in the weeke, that is Friday and Saturday, are especially appointed to fish." We can join hands with our professional brother of three hundred years ago, and lament with him over the price of meat.

One can well believe that the drift of human conduct has not changed much in all these years, when one finds that Coghan waxes warm over those obstinate people who will not avoid infection, on the ground that one will have a disease sooner or later, and it might as well be first as last.

The book shows strikingly how deeply rooted in the past are some common customs of to-day, little things which are so trivial that no one thinks of them in any way but as things of the moment. We all know how often one is told to smell of bread if one tends to sneeze on smelling mustard. The same advice is in this book. And so is the advice to toast cheese before putting it in a trap, the better to entice rats.

The same vanities were then as now, for we find Dr. Coghan remarking on the custom of young girls drinking vinegar to make the complexion pale.

"Cummin seeds sodden in water, if the face be washed with the same, doe cause the face to be clearer and fairer," all of which shows that women, perhaps men too, had an eye to complexions, and were wont to consult a favorite physician on such important matters.

Familiar stories and jokes appear, even in this medical book; the drunkard's wish for a giraffe's throat bobs up, only it is a crane's gullet that is desired this time; and the ostrich story is at hand, but it is the mullet which hides its head when Coghan tells the tale.

As one reads, one finds two particular vanities cropping out, one a national and one an ethnic; Coghan thought, as do many Englishmen to-day, that his country was superior to all others, and there are many expressions in his writings which, through him, exhibit the ethnic belief that man is of different clay from the brute.

Dr. Coghan's long experience as a teacher seems to have fixed in his mind many definite ideas concerning students; they were not a very robust lot and were bothered more or less with weak digestions. He seems to think he knows why so many students fail to achieve success: "The excess of wine is the cause . . . . why few young men that bee students, come to profound knowledge and ripenesse in these days"; and to avoid such a harrowing possibility, the following advice is written: "But I advise all students, such as bee students *nomine et re,* because they have commonly feeble braines, if not by nature, yet through study, to refraine from strong wines, because they distemper the braine, and cause drunkennesse ere a man bee ware." Our worthy author may have been no novice in Bacchus, for he says that cold water hinders digestion because it "cooleth the stomach overmuch. . . . The like effect it hath . . . . . when thirst happeneth after drinking of much wine." One might imagine this candid old practitioner comparing notes with Eugene Field when they met in the Beyond, for Field's verses on the Clink of the Ice in the Pitcher would surely appeal to him. "Katzenjammer" was evidently not an unheard-of thing in Coghan's days.

The book has running through it a vein of piety, which, it seems to me, is quite genuine; notwithstanding this attitude towards things religious, our author does not hesitate to pay his respects to clergymen and priests, in a way which was perhaps not to their liking.

Because of good Wine, more than of any other drink, are engendered and multiplied subtile spirits, clean and pure. And this is the cause (saith hee) why the divines that imagine and study upon high and subtile matters, love to drink good wine.

Assuming that there was no other information available, would this old tome help to throw light on the natural history of England as it was in those days? Indeed it would; it tells us that the wild ox (the present Chillingham Park cattle) and the wild boar still roamed in England; in fact, we can assume that both were common enough to be considered as possible sources of food; we should also learn that deer, hare and rabbits were frequently used as food, though it might bother us a bit to determine what a "conie" was, did not the author use the word synonymously with rabbit. We should learn, too, that paleolithic man's habit of breaking the long bones to extract the marrow had survived to Coghan's time, since we find him writing of the uses of bone marrow as food; by the same page we learn that he did not wholly differentiate between the long bone marrow and the spinal cord, for he says that the "marrow that cometh downe the backe bone is of like nature to the braine."

One of man's most anciently rooted beliefs comes to light again in this volume: An enemy's courage is in his heart, eat his heart and acquire his courage. It is but a step to apply this doctrine to the different organs of animals and the functions of such organs.

"The stones and udders of beastes being well digested doe nourish much, but the stones are better with their moystnesse, the udders cold and flegmaticke, they both doe increase seed of generation." Thus is added one more to the already long list of those who anticipated Brown-Sequard by generations.

Coghan's list of birds, included in the chapters on food, was of especial interest to me, and a very instructive one too; from it we learn that he and his contemporaries knew of, and used as food, "Fesaunt, Partrich, Wood Cock, Pigeons, Turtle Doves, Queales." We see moreover, that this schoolmaster physician believed that "Queales" furnished the meat rained by Jehovah for the Israelites while they wandered upon the desert. We also find that in England, small birds, such as sparrows, were employed for food, as they are to-day in southern and middle Europe, *i. e.,* starlings, blackbirds, lapwings, moor hens, wagtails, robin red-breast, larks. All are birds which most of us nowadays would not only scorn to touch as food, unless driven to it by dire distress, but would feel a pity that such useful and genial species should be killed to so little purpose; many game birds are included in Coghan's list, such as geese, swan, mallard, teal, shoveller, wigeon, plover, and so also many which are quite beyond the pale of civilized beings—herons, cranes, "buttorns" (bitterns). One exotic species, long acclimatized, in England, the peacock, and another, introduced surely not more than half a century before the Haven of Health was written, the turkey, are both mentioned. No one can tell whether Coghan was personally familiar with all the birds in this ample list, or not; we can see, however, that in some respects his ornithology was not much worse than that of White of Selbourne fame, for the latter believed that swallows hibernated in swamp mud during each winter, while the former had a most fantastic conception of the zoölogic relations of the puffin. Let him tell us about this bird: "There is also a kind of fish called a Puffin which in respect that it liveth altogether in the water, may be accounted a fish; whereas otherwise considering that it is feathered and doth flie, as other foules doe, it may seeme to be flesh, except that you would account it as a Syren, or mermayden, that is halfe fish and halfe flesh." Perhaps this was all book knowledge. Who knows?

That England, an island, and a maritime nation, utilized to the utmost its fresh-water, littoral, and deep-sea fishes, and knew them well, is abundantly attested by the list of fishes given in this book. In this list of thirty-nine fishes, there are many which I never heard of, and many others known to me by name only. In addition to this notable list one must add oysters, mussels, shrimps, crabs, lobsters and cockles.

The plants given for foods and medicines make a long enumeration, there being over one hundred, not counting the plant products, fruits, nuts and spices. These various vegetables, fruits, and condiments would betoken, inferentially, a considerable degree of luxury, yet outside of quite circumscribed city and castle circles, all was rough, rude, and

hearty. The rural people met in mass but seldom, and then usually at fairs, when a whole ox might be roasted out-of-doors, the prototype of our Western barbecue. Negative evidence is frequently as interesting as positive; in this long list of vegetable products, compiled and elaborated with evident care, no mention at all is made of the now almost cosmopolitan American products, the potato and Indian corn, probably because then they were only becoming known.

From a medical point of view the key to the whole book is the quotation on the title page; though much of the context of the various chapters may seem silly to us, there still runs through all of the fabric woven by Coghan, a warp of admirable instruction as to diet, drink, and other factors in the preservation of health. In his descriptions of the cooking of foods he shows that the primitive custom of cooking meats and vegetables in earthen vessels still held in England. As one reads his directions about various articles of diet, unexpected facts come to light. It appears that violets were then used as spinach is to-day; one is surprised to find that he seems to have, though something of a *bon vivant* himself, a low opinion of bacon; this may have been because the finished product then was far from what it is to-day.

Astrologic lore crops out when he writes under the caption of "cibus": "Shell fishes be at the best when the moon increaseth as the Poet Horace noteth."

That customs are tenacious of existence, notwithstanding that they be transported across wide seas, and through spaces of time, is shown by the use then, and now, of rice, milk, and cinnamon, all mixed together.

Dr. Coghan's experience made it clear to him that different individuals are suited each to his own kind of exercise or labor. He also carefully differentiated between exercises useful for different parts of the body. Thus he especially commends "tenis," perhaps because Galen had done so, or had at least recommended a game that Coghan called "tenis," and which may have been like modern hand ball.

The extended division on "cibus" is a forceful reminder, in parts at least, that dietetic wisdom did not begin with us and our experimental laboratories. Let us read what Coghan says about the quantity one should eat: "That it be according to the nature of him that eateth, and not always according to appetite. For the temperate stomacke only (which is rare to bee found) desireth so much as it may conveniently digest. Contrariewise the hot stomacke doth not desire so much as it may digest. The cold stomacke may not digest so much as it desireth. Wherefore, the surest way in feeding, is to leave with an appetite, according to the old saying, and to keep a corner for a friend." Surely there is wisdom and good advice in this, even though the same may have been said many times before, and since.

In several places there is expressed a decided preference for fowl, domestic or wild. He sings the praises of "fesaunt" this way: "Fesaunt exceedeth all foules in sweetness and wholesomeness, and is equall to a Capon in nourishing but is somewhat dryer, and is of some men put in a meane between a henne and a partrich. It is a meate for Princes and great estates, and for poore schollers when they can get it."

His classification of diets, you will surely agree with me, is not without humor:

> Full diet is much enough,
> Mean diet is enough in a mean,
> Slender diet is little enough.

There must have run a streak of the epicure through this physician, for he waxes warm over the praises of a good cook and good cooking; "A good cooke is a good jewel and to be made much of, *modo fit vir bonus,*" and this is exemplified again when he writes, "because cookery is part of physicke and a good cooke (as Dr. Broad saith) is halfe a physitian."

When Coghan advises "Poor Schollers" that "Great suppers and late suppers must bee banished from all healthful houses," mayhap he had companies like this in mind. If by chance we eat too much despite his advice, we can find consolation and a present relief in his suggestion that "if thou feel that thou hast eaten too much, arise, goe thy way, cast it out of thy stomacke, and take thy rest, and it shall ease thee, so that thou shalt bring no sickness into thy body."

Last fall a cowboy said to me as I was on a cattle drive, "I believe it does a man good to get drunk once in a while, say once a month," a notion much older than I, at the time, realized, for it is fully amplified in this book, when it says: "Yet I read in *Arnoldus* upon *Schola Sal.* that surfetting and drunkenness is sometimes expedient, because thereby we fall to vomit, whereof ensueth cleansing of the stomacke, and preventing of many ill diseases of long continuance." This notion is not, however, to the satisfaction and approval of Coghan, who once more shows sound sense in matters dietetic when he quotes, with approval, his admired medical forebears:

> But to procure vomit, through excessee and drunkenness, as it is ungodly, so it is beastly; and doth more hurt the stomacke, the braine, the brest, and all parts of the body, than it doth profit. . . . . .

Much as he seemed to have valued wine in moderation and to have condemned it in excess, his opinion of a total abstainer is unique, which I will read to you: "And this is the cause (as I thinke) why men by nature so greedily covet wine; except some od *Abstemius,* one amonge a thousand perchance degenerate, and is of a doggish nature, for dogges of nature doe abhorre wine."

Mingled with his directions how to drink, and how to choose strong drinks, are indications of his notions of physiology, and theories of disease. Thus he says:

> That is to say we ought to drink moderately, so that the stomacke be not hurt thereby, nor drunkennesse caused; for much abundence of drink at meales drowneth the meat eaten, and not onely letteth convenient concoction in the stomacke, but also causeth it to pass faster than nature requireth, and therefore engendreth much flegme, and consequently rheumes, and crudenesse in the veines, debility, and slipperinnesse of the stomacke, continuall flux, and many other inconveniences to the body, and members.

There are many curious sayings in his discourse on milk, which would be of keen interest if read *in extenso,* but we will have to content ourselves with an excerpt or two. Milk, according to him, is blood twice concocted, and it is of great use for "them that bee wasted, or in a consumption, or be leane." For woman's milk he has the highest praise only: "Yet common experience proveth that womans milke sucked from the breast is without comparison best of all in a consumption. Wherof a notable example was shewed of late yeares in the old Earle of Cumberland, who being brought to utter weakeness by a consuming Fever, by means of a womans sucke together with the good counsaile of learned Physitians, so recovered his strength, that before being destitute of heires male of his owne body, he gate that most worthy gentleman that now is inheritour both of his fathers vertues and honour."

While Coghan gives extended space and much attention to strong drinks, and is decidedly not a total abstainer, he also is loud in his praises of water as a beverage; passing over all of this, though it be of real interest, let us read what his tests of a good water are: "First by the lightnesse, for the lightest is best. Secondly by little skim or froth in boyling. Thirdly by drenching of linnen clothes in the water, and laying the same to dry, for that which is soonest dry, sheweth the best water."

This being a modest and polite gathering, and the reader a bashful man, the chapter on Venus will have to be passed over most hastily; Coghan's humor comes to the surface in it, more than in any other one in the book. To digress a moment I may say that in speaking of fishes, he plays on words, and says, "And the tongue of a carp is very pleasant to carping Ladies." Likewise under the head of trout he is again facetious. "This fish by nature loveth flattery; for being in the water it will suffer itselfe to bee rubbed and clawed, and so to bee taken. Whose example I would wish no maides to follow, lest they repent after claps."

One reads with amusement the following disapproval of early marriages:

> that the woman at twelve yeares of age, and the man at fourteene, are marriageable, which thing is the cause that men and women in these dayes, are both weake of body, and small of stature; yea in respect of those that lived but forty years agoe in this land; much more then in comparison of the ancient inhabitants of *Britaine*, who for their tallnesse of stature were called *Gyants*.

The extraordinary sexual capacity of the house sparrow of England must long have been current knowledge in that period, for Shakespeare speaks of it in his plays, and Coghan mentions it in these words:

> And this is the cause why such as use immoderate *Venus* be short lived, and as the Sparrowes, through incontinency, consume themselves.

Along a similar line of thought he cautions against the use of sparrows as food because "they stirre up Venus, especially the Cocke sparrow." Having shown that there are dangers in worshiping too devotedly at the shrine of Venus, he also remarks on the evil effects of being continent.

Perhaps it will be useful to this meeting to learn how to abate carnal lust:

> Last of all to conclude these meanes whereby to abate carnall lust, I will recite certaine examples gathered out of our English Chronicles of some men in time past, who supposed all chastity to consist in single life. *Elphlegus*, Bishop of Winchester, put upon him *Duntanes* a Monkes apparell, that hee might thereby avoid both the fire of concupiscence and the fire of hell. *S. Petrock* an hermit of Cornewall, was faine every night from the crowing of the cock to the spring of the morning to stand naked in a pit of water to abate the movings of his flesh, yet could he never have remedy of that disease, untill he went on pilgrimage to Rome and Ierusalem. *S. Aldelme* Abbot and Bishop of Malmsbury, when hee was stirred by his ghostly enemy to the sinne of the body, would hold within his bed by him a faire maiden so long time as hee might say over the whole Psalter, to the intent to doe the more torment to himselfe and his flesh. These men (as you see) as holy as they seemed, were yet captives to *Cupid*, and could hardly get loosed out of his bands, or whether they were loosed at all, it may be doubted. . . . .

His views, on the other hand, of the beneficial results of exercising this primal function are not without interest: "For it procureth appetite to meate, and helpeth concoction, it maketh the body more light, and nimble, it openeth the pores and conduits, and purgeth flegme, it quickneth the mind, stirreth up the wit, reviveth the senses, driveth away sadnesse, madnesse, anger, melancholy, fury."

It is touching to witness the extreme solicitude this good old chap had for his students and scholars. Thus he says that to abate concupiscence the best, in his judgment, "is for a man to keep himself out of the company of women."

One naturally asks, while and after reading this book, what sort of a physician this man was. We have seen, through the quotation from his biography, that he was esteemed a good physician. Can we find evidence of this in his writings? One cannot be very critical in this attempt, for the avowed purpose of the book in hand, clearly put forth in many places, is along the lines of prophylaxis, and hence it can hardly be expected to show the writer's merits as a clinician.

There was, in Coghan's time, really no science of any sort, much less any systematized knowledge of medicine which, under the most liberal construction, could be called a science of medicine. While the germs of our so-called present-day science of medicine were developing at that time, there had been little or no advance to speak of in the study of medicine, especially in anatomy and physiology, from the third century on to about the time of Coghan's life. He was clearly a follower of Galen, in so far as one can judge from his therapeutics; he used simples, and mentions nowhere in his discourses any inorganic as a medicine, though he knew of Paracelsus, specifically mentioning him on page 180, and presumably knew of his views and of his strong predilection towards salts, and other chemical agents. Moreover we can feel further confident of his admiration of, and faith in, Galen, since he quotes the latter most extensively; he also quotes numerous other older medical writers, being familiar with such parts of

the Arabian school (aside from its Galenic features) as would be transmitted by Avicenna's writings. Whatever he may have thought of the teachings of his own immediate medical predecessors, and contemporaries, we can be sure that he was not misled by the false notion that drugs were a *sine qua non,* though some words of his would imply that he did think medicine was indispensable; he had, unquestionably, great faith in the medical art of his day, but he also clearly discerned that there is such a thing as the *vis medicatrix naturæ.* His book shows in itself, and in its thesis, his appreciation of the surpassing importance of prophylaxis, a thing redounding very much to his credit, when we consider the state of medical knowledge at his period. If, before reading the Haven of Health, one had forgotten all about the humoral theory as expounded by Hippocratic physicians and the temperament theory as held by followers of Galen, he would soon be reminded of these ancient beliefs, by page after page of Coghan's writings. There is, however, less of the humoral theory in the book than of Galen's theory of temperament. Almost everywhere one finds that Coghan, in describing foods, carefully gives the degree of heat or cold, and of moist or dry. "Mallowes are hot and moist in the first degree," whereas caraway "is hot and drie in almost the third degree."

"Concoction" was a well-worn word with him as it was with many of his contemporaries and successors. What we should say was digested he says is "concocted," and as we have already seen, his conception of the secretion of milk has to be expressed by the same word; that is, "milk is made of bloud twice concocted." His knowledge of the character of different parts of certain foods was hazy, and naturally often incorrect. For example he mistook the thermo-coagulable albuminoid of milk for a second kind of cream.

What we term physiology was with him non-existent; nevertheless he tries to explain numerous different physiological processes. On page 279 we have the following example, to wit:

> Now to enter more deepely into the nature of mankinde . . . you shall understand, that as every living creature doth feed, and as the meat received is altered and changed three times, that is to say, in the stomacke, liver, and parts before it nourish the body, and as every concoction hath his superfluity, or excrement, as the stomacke ordure, the liver urine, the veines sweate.

This may sound strange, yet it is simple when compared with his explanation of sleep: "for here is shewed by what meanes sleepe is caused. That is, by vapours and fumes rising from the stomacke to the head, where through coldnesse of the braine, they being congealed, do stop the conduits and wayes of the senses, and so procure sleepe."

The book has many suggestions commanding wholesome respect, advice of help through all time; listen to this: "Man feeds to live, and liveth not to feed. Yet a reasonable time to eat in is nccessary, for to eat overgreedily, and to snatch up our meat hastily, is hurtfull, and hindereth concoction; and to chew our meat well and to swallow it downe leisurely, is a great furtherance to the well digesting of the same. And indeed, it is the very end and purpose why the teeth were ordained."

The following quotation will give some inkling of his beliefs about the digestion of meat, and, too, how the Galenic terms of heat or cold, moist or dry, were applied: "But here in England where we feed on divers sorts of meates at one meale, the order commonly is thus; that first we eate pottage or brothes, then boyled meates, after that rosted or baked, and in the end cheese and fruits. . . . And next I say, that for as much as our stomacks in England most commonly be hot and cholericke, that grosse meats be most convenient to be eaten first."

We to-day eat cheese with pie, because it is a convention; this convention probably arose beeause of the notion that cheese aided in the digestion of pie, and perhaps it is a direct descendant of the belief expressed by Dr. Coghan when he says: "First it [cheese] strengtheneth a weake stomacke. Secondly it maketh other meates to descend into the chief place of digestion, that is the bosom of the stomacke . . . . ."

It is rather difficult to estimate how much he realized the truth of his remarks when he warns against the use of fish taken from muddy waters, and advises the use of fire to destroy contagion. In the brief outline on how to avoid the plague there is much wisdom, and the same may be said of his directions how to avoid gout. Here and there in the book one glimpses a dim conception of immunity: "for they that come out of a pure aire into a corrupt ayre, are in greater danger than they that never fled away."

There is only one attempt in the whole book to describe a disease, a description which, seemingly, gives a picture of an epidemic of typhoid fever occurring in 1522, this date making his description probably a second-hand one.

It is curious how clearly two very divergent strains run through his medical ideas; he is very sound about diet, exercise, moderation, etc., and on the other hand many of his conceptions of therapeutics are ludicrous; perhaps because he could not analyze and separate the effects of drugs, and could check up the good results of proper diet, and exercise; and in all this he probably did not wholly realize how much physicians are aided by nature. Of his mistaken ideas, we may mention his feeling that yellow jaundice and worms are dangerous without medicine, and that a pleurisy is present death "without blood letting."

Many of our contemporaries believe, as he did, in the successful solvent treatment of renal and vesical stone. Perhaps there is truth in this; certainly there seems to be truth in his theory that certain kinds of food predispose to, and promote the formation of, calculi.

Any undue credulity he may have exhibited is excusable, for he lived when there was little or no tendency to study cause and effect; when Coghan writes that sage is of use "because it is good against pleurisies, and comforteth the sinews and Braine, it must needs bee for Students, who are commonly cumbered with diseases of the head," and that hare's brain is good for "shaking of the limmes, which is called Palsie," one must not feel that he is to be classed with the

thin-witted people who built theories of dilutions and potentizations, and their wonderful effects. He was simply repeating the errors which were a heritage from an even more credulous ancestry. We must overlook this, and give him credit for the many sound bits of advice he deals out in this book.

Let us see what kind of a prescription he writes, if what is here given may be called a prescription; these are the directions for making "*aqua composita*":

Take of Sage, Hisop, Rosemary, Mint, Spike, or Lavender leaves, Maierom, Bay leaves, of each like much, of all foure good handfulls, to one gallon of liquor. Take also of Cloves, Mace, Nutmegs, Ginger, Cinamome, Pepper, Graynes, of each a quarter of an ounce, Liquorise and Anise, of each halfe a pound: beate the spices grosse, and first wash the herbs, then break them gently betweene your hands. Use the Liquorise and Anise as said in *Aqua vitæ*, then put all together into a Galon or more of good Ale or Wine, and let them steep all night close covered in some vessell of Earth or Wood, and the next morning after distill them as you doe *Aqua vitæ*.

We look in vain through this work for indubitable evidences of a belief in, or use of, charms and kindred relics of barbaric medicine; there are several passages which imply a belief in astrology, though all of this may have been included on the authority of his predecessors, which would not necessarily carry with it his own personal approbation. As an example of undue faith we may instance his apparent approval of Dr. Steven's Water, a decoction of wine, ginger, galingale, canel, cinamom, nutmeg, greyns, cloves, mace, annis, fenel, caraway, sage, mint, red roses, time, pelletory of the wall, wild maierom, rosemary, wild time, camamel, lavender and avens, all distilled in a "Limbecke" and useful because "It comforteth the spirits, and preserveth greatly the youth of man & helpeth inward diseases comming of cold, against shaking of the palfery, it cureth the contraction of sinews, and helpeth the conception of women that be barren, it killeth worms in the belly, it helpeth the cold gout, it helpeth the tooth ach, it comforteth the stomacke very much, it cureth the cold dropsie, it helpeth the stone in the bladder, and reynes of the backe, it cureth the canker, it helpeth shortly a stinking breath, and who so useth this water now & then, but not too often, it preserveth him in good liking, & shal make one seeme young very long."

There are also hints that there then existed in England relics of very ancient savage medicinal agents; Coghan speaks of the use of the "lungs of fox, pulverized for preserving the lungs," and of an "electury" which he calls "Loche de Pulmon Vulpis"; in an analogous class is a famous remedy long used by orientals, called "Triacle," a compound made under conditions of great mystery and ceremony, and containing, besides many other ingredients, portions of vipers. If one can believe what Coghan said about this remedy, it must have been a boon to suffering humanity. "Yet this much I dare say by the authority of Galen . . . . that no one medicine is better, either to preserve from the plague, or to expell the venome the principall parts in such as be infected, than Triacle, and is not onely good in the plague, but also in all other poysons, and noysome drinks; yea, and in most parts of other diseases, as the Cough, the Cholicke, the Stone, the Palsie, the Jaundice, the Ague, the Dropsie, the Leprosie, the Headache . . . . ."

It would be most unfair to look upon this side of the shield only; if he believed such things, and we cannot be sure he did, nevertheless they did not preclude his having faith in things of manifest helpfulness. He advised the use of cold drinks for fever, which places him far in advance of some medical men who practiced only sixty years ago. He also clearly recognised the very important fact that abstinence from food was indicated in some diseases, for he writes: "Yet in sickness sometimes a slender diet is necessary, especially in *Morbus acutis*"; and he knew that depletion was to be had in several ways. Fasting "is next in force to blood letting."

The chapter on the plague ought to give us some measure as to his abilities as a clinician, but it must be confessed that it reveals little; we can certainly agree with his advice that plague patients should consult, and secure the aid of, learned physicians and surgeons.

Coghan believed thoroughly in the infectivity of plague, through personal channels or fomites, and in the wisdom of avoiding all avenues of infection; there are signs in his writings that he had a more or less clear conception of the fact that there were differing degrees of infectivity.

What shall be said of the book now that it is read? It is surely genuine in its efforts to give good advice, and advice only along the lines put forth in the thesis as being for "all those that have a care of their health," while the generous credits in the text show a total lack of pretentious claims to things not his own.

As for the man, one can say that he creeps into one's affections, an honest, clean and God-fearing figure, endowed with something of the seer in that he felt the predominant importance of prophylaxis, and the value of health.

Without any other characteristics, he would be notable beyond his time and generation in that he clearly recognised that every man is a law unto himself:

So I say, notwithstanding that every rule prescribed in this booke cannot agree with every mans complection, yet the rules are not to bee disallowed, but to bee followed accordingly as every man shall finde them good and wholesome in himselfe. And this is the best Physicke of all for every man, to know thoroughly the state of his own body, and to mark diligently what things are wont to doe him good or harme.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XXII is in progress. The subscription price is $2.00 per year in the United States, Canada, and Mexico; foreign subscriptions $2.50.

NOTES ON NEW BOOKS.

Litora Aliena. By MEDICUS PEREGRINUS. Price, 50 cents. (*Boston: W. M. Leonard, 1911.*)

A small paper bound volume of letters sent to the Boston Medical and Surgical Journal, by one of its editors, while traveling in England and on the Continent. He writes of things medical as well as of objects with other interests, and a pleasant half hour can be spent, when one is tired of serious reading and hard thinking, in glancing through these views of foreign countries with their various attractions.

A Treatise on Diagnostic Methods of Examination. By PROF. DR. HERMANN SAHLI, Director of the Medical Clinic, University of Bern. Edited, with additions, by NATHANIEL BOWDITCH POTTER, M. D., Asst. Professor of Clinical Medicine, College of Physicians and Surgeons, New York. Illustrated. Price, $6.50. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

The admirable work, first reviewed in the BULLETIN, April, 1907, now appears in an enlarged form, improved by the careful editing of the author. This edition is a translation of the fifth German edition, and is therefore fully up to date, and most valuable for all students.

State Board Questions and Answers. By R. MAX GOEPP, M. D., Professor of Clinical Medicine at the Philadelphia Polyclinic. Second Edition Revised. Price, $4.00. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

Questions on serum and vaccine therapy, serum diagnosis and treatment of syphilis, chemotherapy, diseases due to intestinal parasites and other tropical disorders, the new heart-physiology, the myogenic theory and the graphic methods of studying the phenomena of the circulation have been added to this edition. When it first appeared, the book was reviewed in our issue of August, 1908. Except for these new additions the work practically remains as it did then.

The Principles and Practice of Modern Otology. By JOHN F. BARNHILL, M. D., Professor of Otology, Laryngology and Rhinology, Indiana University School of Medicine, and ERNEST DE W. WALES, B. S., M. D., Clinical Professor of Otology, Laryngology and Rhinology, Indiana University School of Medicine. Second edition revised. Illustrated. Price $5.50. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

The merits of this book were commented upon in this journal in May, 1908, its first-class illustrations and "the attention paid to all the little details of clinical study and care of cases." The new edition differs only slightly from the first—some chapters have been rewritten or revised, and with a few additions the book has been made useful by being brought up to date.

A Manual of Physical Diagnosis. By BREFNEY ROLPH O'REILLY, M. D., C. M. Demonstrator in Clinical Medicine and in Pathology, University of Toronto, etc. Illustrated. Price $2. (*Philadelphia: P. Blakiston's Son & Co., 1911.*)

To the medical student about to enter upon his duties as clinical clerk in the hospital ward and to the general practitioner who has become "a little rusty" in the methods employed in diagnosis of a medical case, Dr. O'Reilly's "Manual of Physical Diagnosis" will prove of considerable value.

While numerous books along similar lines have recently appeared, there are several features which make this little book of much practical value.

Beginning with a chapter devoted to the taking of a clinical history the author treats in chronological order the methods employed in the actual examination of a patient. Under "general inspection," we find first noted that which is, as a rule, almost too obvious to mention and for that reason, often overlooked, a careful discussion and tabulation of the various gaits and facies exhibited by the patient.

Special inspection is given to the skin, head and extremities. According to the findings on inspection, palpation, percussion and auscultation each system, respiratory, circulatory and digestive are carefully reviewed.

The chapter devoted to the circulatory system has considerable space given to the instrumental methods of examination and contains much of the newer light thrown on the study of the heart by Dr. James Mackenzie, and also reproductions of his excellent cardiograms. The latter half of the manual is devoted to a fairly comprehensive outline of the ordinary laboratory technique which one needs to use in the examination of a medical case.

J. S. B.

The Racial Anatomy of the Philippine Islanders, Introducing New Methods of Anthropology and Showing their Application to the Filipinos with a Classification of Human Ears and a Scheme for the Heredity of Anatomical Characters in Man. By ROBERT BENNETT BEAN, B. S., M. D., Associate Professor of Anatomy, the Tulane University of Louisiana. With nineteen illustrations reproduced from original photographs and seven figures. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

The Racial Anatomy of the Philippine Islands is the outcome of studies in anatomy begun in the Medical Department of the Johns Hopkins University some years ago which have been continued since wherever the author has found material to study, mostly in the Philippines. In his examination of more than 4000 persons during this investigation he has sought for definite types which, in his judgment, will justify him in distinguishing different races by their anatomical pecularities. These types are recognizable by ear form, cephalic index, nasal index and other factors so that they can be studied by families through several generations in order to establish their hereditary characteristics. He finds two predominant types of races in the Philippines, the "Iberian," which seems to have originated from a mixture of the Spanish, and the native races which he terms the "Primitive." From these, giving rise to a race like the Eurasian in India, by various mixtures and environmental conditions, such as climate, soil and altitude, the author gets a variety of races to which he applies varying names like "Modified Primitive," "Australoid," "Alpine," "B. B. B." (Big-cerebellumed, box-headed Bavarian), "Adriatic," "Cro-Magnon" and Blends—the "B. B. B." and "Cro-Magnon" resembling the Iberian, and the "Alpine" and "Adriatic" resembling the Primitive. The volume contains an account of the author's study of these races in the Philippines in order to determine the proportions which exist in various portions of the Archipelago. We find many interesting details respecting the Benguet, Lepanto and Bontoc Igorots, the criminals and outcasts at Manila, the men and women of Laytay and the men of Cainta. The work of classifying these diverse elements has been done with great care and industry and the author deserves all praise. It seems probable that farther study and larger observations will be required to determine how practical this new method of anthropological study may prove. Its methods are painstaking, thorough and accurate. It is a source of regret to all interested in the subject that ill-health required the author to relinquish his studies in Manila.

The chapter entitled "The Relation of Morphology to Disease" is of extreme interest because of the relation of race form to

disease incidence. Thus, at the Malecon morgue, 70 per cent of the Iberians, 56 per cent of the Blends and 33 per cent of the other types died of tuberculosis, whereas only one Primitive and not a single Australoid died of it. Further investigation showed that the Iberian was much more susceptible to all other diseases than the Primitive. "This may be indicative that the European and Filipino offspring of the Iberian type is less resistant to disease in the tropics than is the aboriginal type on its own soil and in its natural environment." The author infers that a process of breeding out an alien stock is in progress. Although the Iberian stock has been added to the Primitive stock by repeated migrations, it does not retain its vigor when mingled with an aboriginal people in a new environment and succumbs to diseases like tuberculosis more easily than the original stock which has become suited to its habitat.

The author has brought much new and valuable material to aid the study of Anthropology and has added materially to our knowledge of the Filipino races.

New and Nonofficial Remedies, 1911. Containing descriptions of articles which have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association, prior to January 1, 1911. Price, paper, 25 cents; cloth, 50 cents. Pp. 282. (*Chicago: Press of the Americal Medical Association.*)

This book, bound in paper, is furnished free to all members of the American Medical Association, but the reprint in book form is valuable for pharmacists, chemists and others. It differs from the first edition essentially only by the addition of more pages to describe new articles accepted by the Council during 1910. It would, on the whole, seem better than reprinting the entire volume annually to simply publish a small pamphlet of the new articles. The appearance of this work was noted in our issue of June, 1910, and it is a satisfaction to again call attention to this important publication.

Scientific Memoirs. By officers of the Medical and Sanitary Departments of the Government of India. New Series No. 40.
The Destruction of Fleas by Exposure to the Sun. By Captain J. Cunningham, M. D., I. M. S. Price 9d. (*Calcutta: Superintendent Government Printing, India, 1911.*)

In a brief report of some carefully carried-out experiments Dr. Cunningham proves that fleas are rapidly killed in garments when exposed to the sunlight at a temperature of 120° F. That the method of exposing the clothes on a surface of sand may be used with success for this purpose is doubtless a useful discovery, but its practice must be limited. It is well, however, for all sanitarians to have their attention called to this report, as the system advocated is so simple.

Plaster of Paris and How to Use it. By Martin W. Ware, M. D., Adjunct Attending Surgeon, Mount Sinai Hospital, etc. Second edition revised, enlarged and illustrated. Price $1.25. (*New York: Surgery Publishing Company, 1911.*)

The excellence of this manual was called attention to in the issue of this journal of May, 1907. With some slight changes and the addition of more illustrations the author has succeeded in making it still more useful. It is a first-rate practical small handbook on the subject.

The Life History, Function and Inflammation of the Appendix. By Eldred M. Conner, M. A., M. C., F. R. C. S., etc. Price 1/. (*London: John Bale, Sons & Danielsson, Ltd., 1911.*)

In a short lecture delivered in Manchester (Eng.), during this year, the author propounds certain views as to the causation of appendicitis, and the use of the appendix, which seem strange—for instance that one of the great causes of the disease is the use of white bread, since this contains very fine bits of steel—microscopical in size—from the rollers with which the flour is ground. His view of the use of the appendix is that its lymphoid tissue throws out white cells to conquer either bacterial or other invaders. These ideas will require further proof before they can be generally accepted as correct.

International Clinics, Vol. I. Twenty-first Series, 1911. Price $2. (*Philadelphia and London: J. B. Lippincott Company.*)

A paper on pellagra, several on syphilis, two on poliomyelitis, one on typhoid fever, and others on surgery, ophthalmology, physiology, anatomy, biology and tropical medicine, etc., make this volume one of wide interest. In addition to the "Clinics" there is also a review of the "Progress of Medicine During 1910," which adds value to the work. Attention has been drawn so frequently to the character and scope of the "International Clinics," as well as to their merit that a few items of the contents are merely selected to show the variety of topics treated.

Diseases of the Nose, Throat and Ear—Medical and Surgical. By William Lincoln Ballenger, M. D., etc. Third edition. Revised and enlarged. Illustrated. (*Philadelphia and New York: Lea & Febiger, 1911.*)

It is but a year ago since we had the pleasure of noting the appearance of the second edition of this excellent work. The book deserves its success, and the new edition is an improvement on its predecessor. The author has carefully revised his previous work and made it still better for students and practitioners.

Das Radium in der Biologie und Medizin. Von Professor E. S. London, Leiter der pathologischen Abtheilung an K. Institut für experimentelle Medizin zu St. Petersburg. Mit 20 Abbildungen in Text. Preis 6 Mk. (*Leipzig: Akademische Verlagsgesellschaft m. b. H., 1911.*)

This is neither a text-book nor a hand-book, but merely a well-made compilation of the use and value of radium in biology and medicine. Until this pamphlet appeared no one seems to have taken the trouble to extract from the medical literature of all countries the many and varied reports on radium as a therapeutic agent, and here for the first time those who can read German have the opportunity to gather a clear idea of the general consensus of the profession on the uses of radium. The work is divided into A, the physical and clinical properties of radium; and B, the physiological properties of radium. Section B is subdivided into 4 parts as follows: 1. On the mechanism of the action of radium on living bodies; 2. Its action on bacteria, fungi, ferments, toxins and antitoxins, plants and lower orders of animals, process of embryonic development and regeneration, and on individual organs and tissues; 3. The general action of radium and its emanations on the higher orders of living beings; 4 Radium or Emanation therapy. There is a good bibliography, and a few illustrations.

Scientific Memoirs. By Officers of the Medical and Sanitary Departments of the Government of India. New Series No. 39.
The Applicability to Medico-Legal Practice in India of the Biochemical Tests for the Origin of Blood-Stains. By Lieut.-Colonel W. D. Sutherland, M. B., I. M. S. (*Calcutta: Superintendent Government Printing, India, 1910.*)

This is a carefully prepared report, but as the title indicates, of interest only to a small number of the profession. Such experiments as were carried out by Dr. Sutherland add, however, to our general knowledge of biochemical problems, and from this department of the Government of India much valuable information has come.

The Practice of Surgery. By James Gregory Mumford, M. D. Visiting Surgeon to the Massachusetts General Hospital, etc. Illustrated. Price $7.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

The author assumes the reader's preliminary training and therefore omits the consideration of the principles of surgery except incidentally. He endeavors to give an account of the practice of surgery as it is seen in the accident ward and operating room.

The plan of the book is unusual. In order to present the various subjects in their true perspective the author takes up surgical diseases in their order of interest, importance, and frequency, so far as he is able with due regard to sequence. He chooses appendicitis as the subject of the first chapter because appendicitis is the most conspicuous example of acute abdominal disease.

The book is divided into seven parts: I. The Abdomen; II. The Female Organs of Generation; III. Genito-Urinary Organs; IV. The Chest; V. The Face and Neck; VI. The Head and Spine; VII. Minor Surgery, Diseases of Structure.

There are numerous excellent illustrations, and the book is nicely gotten up. Many well-chosen references are given.

It is to be regretted that a number of interesting subjects are so briefly considered. The author has accomplished his purpose of presenting the practice of surgery as surgeons see it, in a most satisfactory way, and the book will be a very welcome and useful addition to the library of the operating surgeon.

J. S. D.

Dislocations and Fractures. By Frederic Jay Cotton, M. D. Illustrated. $6.00 (*Philadelphia and London: W. B. Saunders Company, 1910.*)

Very little need be said in a review of this work. One has only to glance through its pages to realize the thoroughness and detail with which the author has handled his subject. The text is clear and concise and is admirably elucidated by over twelve hundred cuts, every one of which has been selected with the greatest care. Indeed it is hardly necessary to read the text at all, so well do the drawings illustrate the various fractures, dislocations and methods of treatment.

In view of the fact that operative procedures as regards fractures are being looked upon with more and more favor, it is possible that a little more space given to this side of the subject might have added to the usefulness of the book. Dr. Cotton is certainly to be congratulated upon the success of his efforts.

Bertram M. Bernheim.

Diseases of the Skin. By James H. Sequeira, M. D., F. R. C. P., etc. Illustrated. Price, $8. (*Philadelphia: P. Blackiston's Son & Co.*)

Although the price of this book seems large it is well worth the money—the illustrations can hardly be bettered; the photographs are of exceptional excellence, and the "three color" pictures are remarkable in demonstrating certain lesions. But this is not the only merit of the work, which is an excellent text-book for students and the general practitioner. The description of the diseases is clear, concise and simple, and the treatment practical and rational. The author has not dwelt much on the pathology of the lesions, but after all, except for specialists, he has given enough to make it evident to any student what the fundamental underlying changes are due to, so far as is known. The references to the literature are well selected, and the book in all respects seems to be fully abreast of the times. It is certain to be well liked by students.

Year-book of the Pilcher Hospital. (*Brooklyn, N. Y., 1911.*)

The Pilcher Hospital was established a little over a year ago by Dr. Lewis Stephen Pilcher and his sons, and this Year-book is composed of a series of papers dealing with the surgical cases they have treated. Some of the articles have already appeared elsewhere, but a large number are new, and the Year-book, with a few illustrations, some of which are in color, is an evidence of the good work done by the Pilchers, and will be a stimulus to other surgeons, who have private clinics, to publish, either annually or at regular intervals, reports of the work done by them. The Mayos of Rochester have just issued a volume, and both these products are well worthy of note.

Burdett's Hospitals and Charities, 1911. The Year-book of Philanthropy and Hospital Annual. Twenty-second Year. 10/6. (*London: The Scientific Press, Limited.*)

It is always a satisfaction to receive this Annual which contains so much information on hospitals that is of value to all superintendents. The statistics furnished are well arranged and can be easily understood. To Sir Henry Burdett, the editor, a great deal of the progress in hospital administration is due. The life of charity institutions depends on the good management of their finances, and he it is who has so persistently, now for twenty-two years, drawn the attention of hospital administrators to the economies that can be practiced, by showing in comparative statistics, the different sums spent, for the same service practically, in various hospitals. To England his work must have been of incalculable value, and as stated above, superintendents in America can benefit themselves by a careful study of his reports, which are a mine of information on questions relating to hospitals, asylums, sanatoria, etc.

Chemistry of Food and Nutrition. By Henry C. Sherman, Ph. D. (*New York: The Macmillan Company, 1911.*)

Many books appear yearly on this subject and few of them are good, so that it is a real pleasure to call attention to Dr. Sherman's work, which is excellent; a serviceable book for the laity, who have some knowledge about digestion, as well as for students. While not entering too deeply into the chemistry the author gives a thoroughly satisfactory review of the best modern ideas of the metabolism of food in the human body and a clear statement of the proper food requirements for a normal individual. It is reliable and not too long nor too technical. Its success is assured.

Plastic and Cosmetic Surgery. By Frederic Strange Kolle, M. D. Illustrated. (*New York and London: D. Appleton & Co., 1911.*)

The author says the importance of Plastic and Cosmetic Surgery is undeniable and yet the literature on the subject is scanty and widely scattered. His object is to place before the profession a precise treatise on these subjects.

The headings of the chapters are as follows: I. Historical; II. Requirements for Operating; III. Requirements During Operation; IV. Preferred Antiseptics; V. Wound Dressings; VI. Secondary Antisepsis; VII. Anesthetics; VIII. Principles of Plastic Surgery; IX. Blepharoplasty; X. Otoplasty; XI. Cheiloplasty; XII. Stomatoplasty; XIII. Meloplasty; XIV. Subcutaneous Hydrocarbon Protheses; XV. Rhinoplasty; XVI. Cosmetic Rhinoplasty; XVII. Electrolysis in Dermatology; XVIII. Case Recording Methods.

One or two quotations taken at random may be of interest. "Lately a product under the name of antiphlogistin has been used locally (in erysipelatous infection) with excellent results

and its use is to be commended even in local wound inflammation." "Unfortunately, these flaps (whole thickness), if they thrive, contract, leaving uncovered spaces, which must be treated separately or allowed to granulate."

The author has undoubtedly done a considerable service by collecting the literature and classifying it, but it is unfortunate that none of the references are given, although there are seven pages taken up by an index of the names of the authors quoted.

Several admirable original procedures are given and the case recording methods, especially by the making of plaster casts, are of interest.

Considering the object of the book the section on skin grafting is rather disappointing. The most exhaustive chapters are those on Hydrocarbon, Protheses and Rhinoplasty.

The volume is nicely gotten up and the illustrations are excellent. The book will be of especial use for refcrence in comparing the relative values of the plastic operations performed by different surgeons.

J. S. D.

BOOKS RECEIVED.

Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, Rochester, Minnesota, 1905-1909. 8°. 668 pages. 1911. W. B. Saunders Company, Philadelphia and London.

Differential Diagnosis. Presented through an Analysis of 383 Cases. By Richard C. Cabot, M. D. Profusely Illustrated. 1911. 8vo. 753 pages. W. B. Saunders Company, Philadelphia and London.

The Blues (Splanchnic Neurasthenia), Causes and Cure. By Albert Abrams, A. M., M. D. (Heidelberg), F. R. M. S. Fourth edition, revised and enlarged. Illustrated. E. B. Treat and Company, New York.

Inebricty. A Clinical Treatise on the Etiology, Symptomatology, Neurosis, Psychosis and Treatment and the Medico Legal Relations. By T. D. Crothers, M. D. 1911. 8vo. 365 pages. Harvey Publishing Company, Cincinnati, Ohio.

Oxford Medical Publications. Text Book of Massage. By L. L. Despard. 1911. 8vo. 290 pages. Henry Frowde, London; Hodder & Stoughton, London.

Oxford Medical Publications. Handbook of the Surgery of the Kidneys. By W. Bruce Clarke, M. A., M. B. (Oxon.), F. R. C. S. With 5 plates and 50 illustrations in the text. 1911. 8vo. 199 pages. Henry Frowde, London; Hodder & Stoughton, London.

Oxford Medical Publications. Introduction to Practical Organic Chemistry. Including Qualitative and Quantitative Analysis and Preparations, with a Special Appendix on the London University Syllabus, and Schemes of Analysis for Stages 1 and 2 of the Board of Education Syllabus. By A. M. Kellas, B. Sc. (Lond.), Ph. D. (Heidelberg). 1910. 8vo. 204 pages. Henry Frowde, London; Hodder & Stoughton, London.

A Text-Book of Gynæcological Surgery. By Comyns Berkeley, M. A., M. D., B. C. Cantab., F. R. C. P. Lond., M. R. C. S., Eng. and Victor Bonney, M. S., M. D., B. Sc. Lond., F. R. C. S. Eng., M. R. C. P. Lond. With 392 figures in the text from drawings by Victor Bonney, and 16 colored plates. 1911. 8vo. 720 pages. Funk and Wagnalls Company, New York.

Manual of Cystoscopy. By J. Bentley Squier, M. D., and Henry G. Bugbee, M. D. 1911. 12°. 117 pages. Paul B. Hoeber, New York.

Progressive Mcdicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. Assisted by Leighton F. Appleman, M. D., Volume I. March, 1911. 8vo. 355 pages. Lea & Febiger, Philadelphia and New York.

Die akute Leukämie. Von Dr. Albert Herz. 1911. 8vo. 184 pages. Franz Deuticke, Leipzig und Wien.

Diseases of the Nosc, Throat and Ear. Medical and Surgical. By William Lincoln Ballenger, M. D. Third edition, revised and enlarged. Illustrated with 506 engravings and 22 plates. 1911. 8vo. 983 pages. Lea & Febiger, Philadelphia and New York.

Oxford Medical Publications. Cholera and Its Treatment. By Leonard Rogers, M. D., F. R. C. P., F. R. C. S., B. S., I. M. S. 1911. 8vo. 236 pages. Henry Frowde, London; Hodder & Stoughton, London.

Das Radium in der Biologie und Medizin. Von E. S. London. Mit 20 Abbildungen im Text. 1911. 8vo. 199 pages. Akademische Verlagsgesellschaft m. b. H., Leipzig.

Medico-Chirurgical College. Contributions from the Department of Neurology and the Laboratory of Neuropathology for the Years 1908-9-10. (Reprints) Volume I. [1911.] 4to. Philadelphia.

Vicious Circles in Disease. By Jamieson B. Hurry, M. A., M. D. (Cantab.). With illustrations. 1911. 8vo. 186 pages. P. Blakiston's Son & Co., Philadelphia.

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BULLETIN

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ZABDIEL BOYLSTON, INOCULATOR, AND THE EPIDEMIC OF SMALLPOX IN BOSTON IN 1721.

By Reginald H. Fitz, M. D., Boston, Mass.

The recent centennial celebration, January 6, 1911, of the Boylston Medical Society of the Harvard Medical School, directly leads to the thought who was Boylston whose name is so intimately connected in Massachusetts with towns, buildings, libraries, schoolhouses, corporations, associations, streets, railroad stations, charities, professorships and prizes? "A name," according to John Quincy Adams,[1] "which if publick benefits can impart a title to remembrance, New England will not easily forget: a name to the benevolence, publick spirit and genuine patriotism of which this University, the neighboring metropolis, and this whole nation have long had, and still have many reasons to attest: a name, less distinguished by stations of splendour, than by deeds of virtue; and better known to this people by blessings enjoyed than by favours granted: a name, in fine, which if not encircled with the external radiance of popularity brightly beams with the inward lustre of beneficence."

The Boylstons thus eulogized were members of a family descended[2] from Thomas Boylston, who at the age of twenty years came to this country in 1635 and settled in Watertown, Massachusetts. His son Thomas, born in 1644-5, married Mary Gardner of Muddy River, then a part of Boston, but set off in 1705 as the town of Brookline. This Thomas was the earliest physician and surgeon of Muddy River and died in 1695 at the age of fifty. It is unknown where and how he received his medical training, unless, in part, in the Narragansett War in which he is reported to have been engaged. There is, however, no verification of the statement by Thacher[3] that he was a native of England and obtained the degree of Doctor of Medicine from Oxford. In his married life of thirty years there were born to him twelve children, the sixth being Zabdiel Boylston, who has gained undying fame as the founder in this country of inoculation as a preventive of the disastrous results of smallpox. Although other descendants of the first Thomas Boylston, through their benefactions and achievements, have been more immediately concerned with conferring popular distinction upon the name, it is especially among physicians that the name and fame of Boylston should be connected closest with the memory of this most meritorious physician of his day in America. This is all the more fitting since his nephew Thomas Boylston and his grandnephew, Ward Nicholas Boylston, in announcing their medical benefactions and gifts call particular attention to the great service rendered to humanity by their kinsman. Thomas Boylston's intended benefactions proved valueless in consequence of business reverses which caused the loss of his fortune. Ward Nicholas Boylston, the wealthy merchant, became a patron of medical education through his gifts to Harvard University, and the medical student's society is his namesake. Zabdiel Boylston, however, was a medical hero, of service to all mankind and his example should ever be memorable.

[1] Inaugural oration, when installed Boylston Professor of Rhetorick and Oratory, in June, 1806.

[2] The Vinton Memorial, 1858.

[3] American Medical Biography, 1828, I, 185.

Zabdiel Boylston was born in 1679 and died in 1766 in his eighty-seventh year. He was educated in medicine by his father and by Dr. Cutler, a physician of some note in Boston. He was not a graduate of Harvard College, from which his eldest son Zabdiel was graduated in 1724, afterwards going to England, where he died. Dr. Boylston attracted no especial attention until 1721. He then was living near Dock Square, not far from the residence of the Reverend Benjamin Colman,[4] pastor of the Brattle Street Church, who refers to "my house (which faces into the Doctor's yard)" and from which he was able to observe the behavior of the doctor's patients. At this time he was presumably one of the practitioners of medicine referred to by Dr. Douglass,[5] who states that there were fourteen apothecary shops in Boston and that every practitioner dispensed his own medicines. Indeed, he is called[6] an apothecary by an anonymous writer not friendly disposed to his cause. It is evident, however, from a communication to the *Boston News-Letter* of July 17-24, 1721, No. 912, signed W. Philanthropos, but written in the manner of Dr. Douglass, that his practice was also surgical. In this he is called a "*Cutter for the Stone*" and is spoken of as illiterate, ignorant and the producer of a "*dangerous quack advertisement,*" with but little experience in smallpox and without having at the time a patient with the smallpox under his charge.

Further evidence of Dr. Boylston's surgical qualifications is to be found in the Province Laws.[7] In these it appears that in 1707 he treated Captain Gridley for a broken arm accidentally received while in the expedition to Nova Scotia. In the same year he treated Mary Lyon, "grievously wounded by a Negroe Man," and in 1712 he cared for Joseph Smith, a soldier in the "late designed expedition to Canada." But whatever may have been the other medical or surgical qualifications of Dr. Boylston, they are wholly subordinate to his great work in beginning and continuing the inoculation of smallpox.

Towards the end of April, 1721, Boston for the sixth time was invaded by this disease. It had then a population of about 11,000. Aeneas Salter, at the close of the epidemic, was employed by the selectmen to make a scrutiny of the inhabitants and found[8] "that the number of persons who continued in Boston (many fled into the country) were 10,567, whereof about 700 escaped; the small-pox decumbitents had been 5,989, whereof 894 died, which is nearly one in seven." Of the previous epidemics that of 1678 had been especially fatal and that of 1702 was of recent memory to many of the inhabitants. Since 1702 the population had nearly doubled in number and a generation of unprotected children had been born. It was announced in the *Boston News-Letter* of April 13-17, 1721, No. 893, that twenty or thirty deaths from smallpox were taking place daily at Barbadoes. In the following week it was stated[9] that the Saltertudas fleet had arrived bringing the disease to the town. Sewall writes in his diary:[10]

April 15th. . . . . Hold another Council about giving Liberty to Mr. Frizzle's Ship from Salt-Tartuda (Tortugas) to come up.

On the 8th of May it is learned:[11]

. . . . whereas a Certain Negro man is now Sick of the Smal pox in the Town who came from Tertudos in His Majesties Ship Seahorse which renders it very likely that that distemper may now be on board that Ship. Therefor for the preservation of the Inhabitants of this Town,

Voted that John Clark, Esqre., be Desired to go on board his Majesties Ship Seahorse and Report in what State of health or Sickness the Ship's Company are in, Espetialy with respect to the Smal Pox or other Contagious Sickness.

There being a negro servant sick with smallpox at the house of Captain Paxton, near the South Battery, the first infected, a nurse was ordered to attend the patient and a watch was placed at the door. On the 12th of May it is recorded that the Seahorse is infected with smallpox and the greater part of its company were on a cruise. "Sundry other Sick on Shore, So that there is not aboue ten or fifteen Effective men on Board." The ship was ordered to Bird Island to prevent the spread of the infection. A town-meeting was held on this day and it was voted[12] to seek the advice of the Governor and Council with reference to sending the Seahorse with its two or three cases of smallpox to Spectacle Island, "Pursuant to a Law of this Province to prevent (God willing) the Spreading of the Smal Pox in this Town & Province."

By the middle of May, when the ship Francis left for London, she carried the report that the disease was rife, although in the *News-Letter* of May 15-22, 1721, No. 898, it was stated that on the 20th of May there was but one case and that in the house where the disease first appeared. Nevertheless, a committee appointed to prepare instructions for the Boston representatives in the coming session of the General Assembly proposed,[13] May 22, 1721, among other recommendations,

"That they promote some further Law Effectually to enable the Select men of Each Town to prevent the spreading of any Infectious Sickness among them." A week later it was admitted[14] that on May 27 there were eight cases of the disease, one in Bennett street, three in Tremont street, two in School street, one in Batterymarch street and one in Winter street. On the 5th of June the school was transferred[15] to the Representatives' room in the Town-House.

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[4] Some *Observations on the New Method* of Receiving the Small-Pox by *Ingrafting* or *Inoculating*. By Mr. Colman, 1721.

[5] Proc. Mass. Hist. Soc., I, 2d Series, 1884-85, 44.

[6] *A Letter* from one in the Country, to his Friend in the City: In Relation to their Distresses occasioned by the doubtful and prevailing Practice of the Inoculation *Of The* Small-Pox, 1721, 3.

[7] The Acts and Resolves of the Province of Massachusetts Bay, Vols. VIII and IX.

[8] *A Summary*, Historical and Political, *of The* First Planting, Progressive Improvements, and Present States of the *British* Settlements in *North America*. William Douglass, M. D., MDCCLX, Vol. II, 396.

[9] *Boston News-Letter*, April 17-24, 1721, No. 894.

[10] 5 Mass. Hist. Coll., 7, 288.

[11] Selectmen's Minutes, 1721, 81.

[12] Boston Town Records, 1721, 154.

[13] Boston Town Records, 1721, 154.

[14] *News-Letter*, May 22-27, 1721, No. 899.

[15] Selectmen's Minutes, 1721, 83.

The epidemic increased in severity and raged throughout the fall and winter till the following January. The disease extended also to the neighboring towns, especially to Roxbury, Charlestown and Cambridge. In Charlestown it was reported [16] that there were "lately" 100 deaths and that there were not more than ten or twelve families which had not suffered from smallpox.

The physicians of Boston at that time whose names have come down to us, were Drs. Archibald, Boylston, Clark, Cutler, Dalhonde, Davis, Douglass, Perkins, Williams and White. Of these Drs. Clark, Douglass and Williams were liberally educated, Clark and Williams being graduates in Arts of Harvard College. Dr. Archibald had been surgeon of an English warship, Dr. Dalhonde was a Frenchman who had seen service in foreign wars, and Dr. Cutler was favorably mentioned by the leading clergymen, while Dr. Perkins was a pious neighbor of Cotton Mather and of satisfactory skill. Several of these physicians in after years were members of the first medical society established in this country.

At the outset of the epidemic the best educated physician of the town was Dr. William Douglass, a Scotchman of about thirty years of age who had been in Boston some three years and had brought letters of recommendation to Increase and Cotton Mather and to Benjamin Colman. These gentlemen spoke well of him and were of some help to him, although but little general notice was taken of him until he made himself known through his opposition to inoculation. He had received his education in Edinburgh, Paris and Leyden and was the only physician in Boston at the time who had received the degree of Doctor of Medicine, although it does not appear when and where he obtained it. He was a well-read man of intelligence and ability, but was conceited, injudicious, inaccurate and contentious. Dr. Samuel A. Green [17] regards him as "a man of fine intellectual parts and a versatile writer. He knew astronomy and could calculate eclipses; he had a taste for natural history, and was withal an excellent botanist. He studied his medical cases, and took careful notes by the bed side."

In the earlier part of his career, with which we are especially concerned, his failings were more conspicuous than his virtues. A forceful man he soon attained an influential position among his fellows. At first he was favored by the ministers, but as he lost their esteem he became a bitter and violent opponent of their views. According to the Reverend Peter Thacher,[18]

> The greater part of the physicians in town & those of most eminence reprobated inoculation in the strongest terms. Douglass placed himself at the head and did not hesitate to use any weapons lawful or unlawful to destroy his antagonists. This man, who had in perfection the hungry penetration and the unrelenting bitterness of his native country (not America), left no method untried to load Dr. B. with obloquy and prevent the success of his practice.

[16] *New England Courant*, Jan. 15-22, 1722, No. 25.

[17] History of Medicine in Massachusetts, a Centennial Address delivered before the Massachusetts Medical Society at Cambridge, 7 June, 1881.

[18] *Massachusetts Magazine*, 1789, I, 776.

Early in the epidemic he was apparently on good terms with Cotton Mather and had lent him certain numbers or a volume of the Philosophical Transactions published by the Royal Society, of which, at the time, he appeared to have had the only copy in Boston. Later another copy was obtained by John Campbell, publisher of the *News-Letter*, although he did not make its presence known [19] until five months after he had received it.

The volume was entitled "Philosophical Translations, Giving Some Account of the Present Undertakings, Studies and Labours of the Ingenious in Many Considerable Parts of the World. Vol. XXIX, for the Years 1714, 1715, 1716. London, 1717."

It may be that Douglass supposed that Mather's interest would lie especially in article IV of No. 339 for April, May and June, 1714, entitled, "An Extract of Several Letters from Cotton Mather, D. D., to John Woodward, M. D., and Richard Waller, Esq., S. R. Secr." There were twelve of these letters on various subjects communicated in 1712. Mather's attention, however, was fixed on article V, "*An Account* or *History*, of the *Procuring* the SMALL POX *by Incision* or Inoculation: As *it has for some time been practised* at Constantinople. *Being the Extract of a Letter* from Emanuel Timonius, Oxon. & Patav., M. D., S. R. S., *dated* at Constantinople, December, 1713. *Communicated to the* Royal Society by John Woodward, M. D., Profes. Med. Gresh. *and* S. R. S." He also undoubtedly studied with care article No. 347 for the months of January, February and March, 1716, entitled, "Nova & TUTA Variolas *excitandi per Transplantationem Methodus nuper inventa & in usum Tracta: Per* Jacobum Pylarinum, Venetum, M. D., & *Reipublicae* Venetae *apud* Smyrnenses nuper *Consulem.*" These articles gave a statement of the method and successful result of the treatment of smallpox in Turkey and neighboring countries by inoculating healthy individuals with the disease.

Cotton Mather was quick to see the bearing of these articles on existing conditions, and the following entry appears in his published diary, for excerpts from which I am indebted to Mr. Worthington C. Ford, of the Massachusetts Historical Society:

> May 26, 1721. G. D. The grievous Calamity of the *Small-Pox* has now Entered the Town. The practice of conveying and suffering the *Small-pox* by *Inoculation* has never been used in *America*, nor indeed in our Nation. But how many Lives might be saved by it, if it were practised. I will procure a Consult of our Physicians, and lay the matter before them.

He prepared a letter to the physicians of Boston, giving an abstract [20] of these communications and suggesting some action. As this letter was the beginning of the battle which raged so

[19] *News-Letter*, 1722, March 5-12, No. 945.

[20] To be found in "Some ACCOUNT of what is said of Inoculating or Transplanting the Small Pox by the Learned Dr. *Emanuel Timonius*, and *Jacobus Pylarinus*. With Some Remarks thereon. To which are added, A Few *Quaeries* in Answer to the Scruples of many about the Lawfulness of this Method. Published by Dr. Zabdiel Boylston, 1721."

violently the following extract from it is taken. "A Vindication of the *Ministers* of Boston from the *Abuses* and *Scandals* lately cast upon them in Diverse Printed Papers. 1722, 7."

I will only say (writes the Doctor) that inasmuch as the Practice of suffering and preventing the *Small-Pox* in the way of Inoculation has never yet (as far as I have heard) been introduced into our *Nation;* where there are so many that would give *great Sums*, to have their Lives insur'd, from the *dangers* of this dreadful *Distemper*, nor has ever any one in all *America* ever yet, made the tryal of it (tho' we have several *Africans* among us, as I now find, who tryed it in their own *Country*) I cannot but move that it be *warily* proceeded in. I durst not yet engage, that the *Sucecss* of the tryal here will be the same, as has hitherto been in the other *Hemisphere*. But I am very confident, no person would miscarry in it, but what must most certainly have miscarried upon taking it in the *Common way*. And I would humbly *advise* that it be never made, but under the management of a Skilful Physician who will wisely prepare the Body for it before he performs the Operation. *Gentlemen*, my *request* is, that you would *meet for a Consultation* upon this Occasion, and to *deliberate* upon it, that whoever first begins this practise, (*if you approve that it should be begun at all*) may have the concurrence of his *worthy Brethren* to fortify him in it.

This letter was dated June 6, 1721, and was directed to one of the physicians, a preacher and also "A Worthy Schoolmaster[21] (whom we did not reproach for going out of his Line for practising Physick)," with the request that he should communicate it to the physicians, with a separate note to one or two of them, and with the express request that Dr. Douglass should not be forgotten but should receive a copy of the letter. The latter gentleman evidently was aggrieved that Cotton Mather, a clergyman, should borrow his books and select therefrom communications upon a medical subject and recommend them to the consideration of the physicians of Boston without consultation with the owner of the books in question. He intimates[22] that before the physicians could meet, consult and report Dr. Boylston had been induced privately to make the trial. Nevertheless, there was no reply from the physicians nor did they hold a meeting, and it is probable that Dr. Douglass was exerting his influence against any action. In the meantime a watch was being set in accordance with the order of the Selectmen[23] of May 6, 1678, to control the removal of infected articles and to prevent the premature appearance in public of the patients. But the epidemic was spreading so rapidly that the guards were being taken from the infected houses as of no use. Persons, among others, Mrs. Boylston, were leaving the town to avoid the risk of contagion. Cotton Mather is filled with great anxiety with regard to two of his children who are liable to acquire the disease. He cannot make up his mind to send them away. He writes in his diary on June 13, "What shall I do with regard unto *Sammy?* He comes home when the small-pox begins to spread in the neighborhood; and he is lothe to return unto *Cambridge.*" His daughter Lizy was in greater fear of the disease than her brother. June 22 he records: "I prepare a little Treatise on the *Small-Pox;* first awakening the Sentiments of *Piety,* which it calls for; and then exhibiting the best Medicines and Methods, which the world has yett had for the managing of it; and finally adding the New Discovery, to prevent it in the way of Inoculation. It is possible that this Essay may save the *Lives,* yea, and the *Souls* of many People. Shall I give it unto the Booksellers? I am waiting for Direction." It would appear from the diary that he made another attempt to interest the physicians for it is written June 23: "I write a letter unto the Physicians, entreating them, to take into consideration the important Affairs of preventing the *Small-pox* in the way of Inoculation."

One of these letters was sent to Dr. Boylston and is reprinted[24] in a memorial of him by the Reverend Peter Thacher, of Brattle Street Church. It reads as follows:

June 24, 1721.

Sir,

You are many ways endeared unto me, but by nothing more than the very much good which a gracious God employs you and honours you to do to a miserable world.

I design it, as a testimony of my respect and esteem, that I now lay before you, the most that I know (and all that was ever published in the world) concerning a matter, which I have been an occasion of its being pretty much talked about. If upon mature deliberation, you should think it advisiable to be proceeded in, it may save many lives that we set a great value on. But, if it be not approved of, still you have the pleasure of knowing exactly what is done in other places.

The gentlemen, my two authors, are not yet informed, that among the [illegible] 'tis no rare thing for a whole company, of a dozen together to go to a person sick of the small pox, and prick his pustules, and inoculate the humour, even no more than the back of an hand, and go home and be a little ill, and have a fever, and be safe all the rest of their days. Of this I have in my neighbourhood a competent number of living witnesse.

But see, think, judge; do as the Lord our healer shall direct you, and pardon this freedom of, Sir,

Your hearty friend and Servant

Co. Mather.

Dr. Boylston.

This letter must have had a very decisive effect on Dr. Boylston's conduct. He was aware that in virtue of his occupation his household was especially exposed to contagion. Intelligent, experienced, skilful, encouraged and supported by an influential citizen of the town, with the undaunted courage accredited to him by Dr. Douglass, he undertook the experiment of inoculation on the 26th of June, 1721. He could not inoculate himself, apparently for the reason that he had suffered from smallpox in 1702, but he was so convinced of the merits of the operation that he inoculated his son Thomas, six years of age, and two of his negro slaves, Jack, thirty-six years old, and Jackey, two and one half years old. According to Hutchinson,[25] "Inoculation was introduced upon this oc-

[21] Presumably Dr. Nathaniel Williams, H. C., 1693, and master of what became eventually the Boston Latin School.

[22] The Abuses and Scandals of some late *Pamphlets* In Favour of Inoculation of the Small Pox, Modestly obviated, and Inoculation further consid'd in a Letter to A.... S...., M. D. & F. R. S., in London, 1722.

[23] Boston Town Records, 1678, 119.

[24] Massachusetts Magazine, 1789, I, 778.

[25] History of the Province of Massachusetts Bay, 1767, II, 273

casion, contrary to the minds of the inhabitants in general, and not without hazard, to the lives of those who promoted it, from the rage of the people." Against Dr. Boylston "the vulgar were enraged to that degree that his family was hardly safe in his house and he often met with affronts and insults in the streets. . . . . Many sober, pious people were struck with horror, and were of opinion that if any of his patients should die, he ought to be treated as a murderer." I find no confirmation of the statement of Thacher[26] that parties with halters threatened to hang him to the nearest tree and that he was obliged to remain secreted for fourteen days in his house in a place known only to his wife and that a handgrenade was thrown into a room occupied by his wife and children. He distinctly states that his wife was out of Boston at the time of his first inoculations and makes no mention of any specific insult offered him either by halters or grenades. As Thacher acknowledges his obligation to Ward Nicholas Boylston, a grandnephew of the inoculator, for information and as the latter was a youth of seventeen at the time of Dr. Boylston's death, it is possible he may have obtained from him an account of personal experiences which were not recorded at the time. Cotton Mather's diary, however, gives a contemporaneous statement of the behavior of the people.

July 16: G. D. At this time I enjoy *an unspeakable* Consolation. I have instructed one Physician in the New Method used by the *Africans* and *Asiaticks*, to prevent and abate the Dangers of the *Small-Pox*, and infallibly to save the Lives of those that have it wisely managed upon them. The Destroyer, being enraged at the proposal of any Thing, that may rescue the Lives of our poor People from him, has taken a strange Possession of the People on this Occasion. They rave, rail, they blaspheme; they talk not only like Ideots but also like *Franticks*, And not only the Physician who began the Experiment but I also am an Object of their Fury; their furious Obloquies and Invectives.

July 18: G. D. The cursed Clamour of a People strangely and fiercely possessed by the Devil, will probably prevent my saving the lives of my Two Children, from the Small-pox in the way of Transplantation.

The outcry against the inoculations was such that Dr. Boylston felt the need of a public statement which should justify his conduct, and he makes the following announcement[27] in the course of three weeks after his first experiment:

I have patiently *born with abundance of Clamour and Ralary, for beginning a new Practice here, (for the Good of the Publick) which comes well Recommended from Gentlemen of Figure & Learning and which well agrees to Reason*, when *try'd & duly consider'd*, viz., *Artificially giving the Small-Pocks*, by *Inoculation, to One of my Children*, and *Two of my Slaves. in order to prevent the hazard of Life, which is often indanger'd and lost by that Distemper in the Common way of Infection: . . . . until the third Day, my little Son's Fever with the rage of the People, sufficiently affrighted me, but I no sooner us'd means, but the Fever abated and the Small-Pocks came* out. . . . . *And in a few Weeks more, I hope to give you some further proof. And as the Thing was new & for fear of erring in doing, I left it wholly to Nature, which needed no help in my Negro Man, who was taken in a day or two before the other two in which time the Symptoms abating, caus'd me to hope for the same in the others.*

Although twice called to account by those in authority for continuing the practice, he inoculated his son John, thirteen years of age, on the 17th of July, and four days later had seven inoculated patients under his care whom he invited his fellow-physicians to inspect. But one of them, Dr. White, accepted the invitation. It was now that the abusive letter already referred to and signed by W. Philanthropos appeared in the *News-Letter* as a criticism of Dr. Boylston's communication. It credited Cotton Mather with "a Pious & Charitable design of doing good" but had only contempt for Dr. Boylston. Within a few days a reply appeared[28] signed by the so-called inoculation-ministers. It reads as follows:

To the Author of the Boston News-Letter.

Sir

It was a grief to us the *Subscribers*, among Others of your Friends in the *Town* to see Dr. *Boylston* treated so unhandsomely in the *Letter* directed to you last Week, and published in your Paper. He is a *Son* of the Town whom Heaven (we all know) has adorn'd with Some very peculiar *Gifts* for the Service of his Country, and hath signally own'd in the successes which he has had.

If Dr. *Boylston* was too suddenly giving into a new Practice and (as many apprehend) dangerous Experiment, being too confident of the Innocence and Safety of the Method, and of the Benefit which the Publick might reap thereby; Altho' in that Case we are highly obliged to any Learned and Judicious Person who kindly informs us of the hazard and warns against the practice; yet what need is there of injurious Reflections, and any mean detracting from the known worth of the *Doctor?* Especially how unworthy and unjust (not to say worse) is it to attempt to turn *that* to his reproach, which has been and is a singular honour to him, and felicity to his Country? We mean those words in the Letter—*A Certain Cutter for the Stone* —Yes, Thanks be to *God* we have such a One among us, and that so many poor *Miserables* have already found the benefit of his gentle and dextrous Hand. We that have stood by and seen his tenderness, courage and skill in that hazardous Operation cannot enough value the *Man* and give praise to *God*. And we could easily speak of *other Cases* of equal hazard wherein the Dr. has serv'd with such Successes as must render him Inestimable to them that have been snatch'd from the Jaws of Death by his happy hand.

The Town knows and so does the Country how long and what *Success* Dr. *Boylston* has practis'd both in *Physick* and *Surgery;* and tho' he has not had the honour and advantage of an *Academical* Education, and consequently not the *Letters* of some *Physicians* in the Town, yet he ought by no means to be call'd *Illiterate*, ignorant, &c. Would the Town bear that Dr. *Cutler* or Dr. *Davis* should be so treated? No more can it endure to see *Boylston* thus spit at. Nor has it been without considerable *Study*, expence in *travel*, a good *Genius*, diligent Application and much Observation, that he has attained unto that Knowledge and successful practice, which he has to give thanks to God for; and wherein we pray God that he may improve and grow with all humility.

The meanwhile we heartily wish that Men would treat one another with decency and charity, meekness and humility as becomes fallible creatures, and good Friends to one another and their Country.

As to the *Case of Conscience* referr'd to the *Divines*, we shall

[26] Op. cit., 187.

[27] *Gazette*, July 10-17, 1721, No. 85.

[28] Gazette, July 27-31, 1721, No. 88.

only say—What *Heathens* must they be, to whom *this* can be a question.

"*Whether the trusting more the extra groundless Machinations of Men, than our Preserver in the ordinary course of Nature, may be consistent with that Devotion and Subjection we owe to the All-wise Providence of God Almighty.*"

Who knows not the profanity and impiety of trusting in *Men* or *Means* more than in God? be it the best learn'd men or the most proper Means? But we will suppose what in fact is true among us at this Day, that Men of Piety and Learning after much *Serious tho't* have come into an Opinion of the Safety of the saulted method of *Inoculating the small pox;* and being perswaded it may be a means of preserving a Multitude of lives, they accept it with all thankfulness and joy as the gracious Discovery of a *Kind Providence* to Mankind for that end:—And then we ask, Cannot they give into the method or practice without having their *devotion and subjection to the Al-wise Providence of* God *Almighty* call'd in question? Must they needs *trust more* in *Men than in their Great Preserver* in the use of *this means* than of any other? What wild kind of Supposition is this? and the *Argument* falls with the *Hypothesis* in our *Schools.*

In a word, Do we not in the use of all means depend on GOD's *blessing?* and *live* by that alone? And can't a devout heart depend on God in the use of *this* means, with much Gratitude, being in the full esteem of it? For, what hand or art of *Man* is there in this Operation more than in *bleeding, blistering* and a Score more things in *Medical use?* which are all consistent with a *humble Trust in our Great preserver, and a due Subjection to His All-wise Providence*

Increase Mather.
Cotton Mather.
Benjamin Colman.
Thomas Prince.
John Webb.
William Cooper.

The above communication somewhat modified to meet with the approval of the other signers was written by the Reverend Benjamin Colman, whose original manuscript has been given to the Boston Medical Library by Dr. F. C. Shattuck. Its historical importance is such that Mr. Colman's letter is printed as originally written, at the close of this article.

Dr. Boylston was now a third time called to task[29] and a meeting of the authorities and the selectmen of Boston was held[30] July 21, 1721, "In Relation to the operation called Inoculation lately practiced in this Town by Dr. Boylston of this Place."

The sensational feature of this meeting was the testimony of Dr. Dalhonde who asserted that four out of thirteen soldiers inoculated at Cremona had died, Six recovered with "abundance of Trouble and Care" and three were unaffected. On opening one of the fatal cases the "Diaphragm was found livid, the Glans of the Panerease tumify'd and the Caul gangreen'd." He stated that he had treated in Flanders a patient with smallpox who claimed to have previously been inoculated five or six times, and whom he believed was incurably lame after his recovery. Of two Muscovite soldiers inoculated in Spain one recovered and the other at the end of six weeks "was seiz'd with a Frenzy, swelled all over his Body, ... his Lungs were found ulcerated, from whence they concluded that it was the Effect of that Corruption which having infected the Limphæ did throw itself upon that Vital Part which occasion'd his sudden Death."

At the same meeting the Practitioners of Physick and Surgery presented the following series of resolutions which were based apparently on the testimony of Dalhonde, and condemned the practice:

It appears by numerous Instances, That it has prov'd the Death of Many Persons soon after the Operation, and brought Distempers upon many others which have in the End prov'd deadly to 'em.

That the natural tendency of infusing such malignant Filth in the Mass of Blood, is to corrupt and putrify it, and if there be not a sufficient Discharge of that Malignity by the Place of Incision, or elsewhere, it lays a Foundation for many dangerous Diseases.

That the Operation tends to spread and continue the Infection in a Place longer than it might otherwise be.

That the continuing of the Operation among us is likely to prove of most dangerous Consequence.

According to Dr. Douglass[31] the Selectmen accepted this view and forbade further inoculation, but Dr. Boylston persisted "in *Contempt* of the Magistrates and in Contradiction to the Practitioners." Dr. Dalhonde's letter was published and aroused anew the fears and wrath of the people, many of whom were in a state of terror lest the disease should be extended through the community by inoculation. According to Cotton Mather,[32] "A Satanic fury raged, the town was still possessed with the Devil" and the writer was vilely abused "for nothing but instructing our base Physicians how to save many precious Lives." The Reverend Peter Thacher states:[33] "It is not many weeks since the author of this account was informed by one of his [Dr. Boylston] childrens (three of whom are still living) of the expression of pious calmness and trust in God, which he was wont to drop when his family trembled at his leaving his house, for fear that he should be sacrificed to popular fury, and never visit it again." For a fortnight no further inoculations were made, and then they were resumed to be continued in increasing numbers till the end of the epidemic.

Cotton Mather writes:[34]

G. D.—Full of Distress about Sammy. He begs to have his Life Saved, by Receiving the *Small-Pox*, in the way of *Inoculation*, whereof our Neighbourhood has had no less than Ten Remarkable Experiments; and if he should after all dy by receiving it in the Common way, how can I answer it? On the other Side, our People, who have Satan remarkably filling their Hearts and

[29] An Historical *Account* of the *Small-Pox Inoculated* in *New England*, Upon all Sorts of Persons, *Whites Blacks* and of all Ages and Constitutions. With Some account of the Nature of the Infection in the Natural and Inoculated Way, and their different effect on Human Bodies. With some *Short Direction* to the *Unexperienced* in this Method of Practice. Humbly dedicated to her Royal Highness the Princess of Wales by *Zabdiel* Boylston, Physician. London, MDCCXXVI, 61.

[30] See Appendix to the Historical Account.

[31] The *Abuses* and *Scandals*, etc., 9.

[32] MS. Diary, July 27, 1721.

[33] Loc. cit.

[34] MS. Diary, Aug. 1.

their Tongues, will go on with infinite Prejudices against me and my Ministry, if I suffer this Operation upon the Child: And be sure, if he should happen to miscarry under it, my Condition would be insupportable.

His Grandfather advises, That I keep the whole Proceeding private, and that I bring the Lad into this Method of Safety.

August 15. G. D. My dear *Sammy*, is now under the Operation of receiving the *Small-Pox* in the way of Transplantation. The Success of the Experiment among my Neighbours, as well as abroad in the World, and the urgent calls of his Grandfather for it, have made me think, that I could not answer it unto God, if I neglected it. At this critical Time, how much is all Piety to be press'd upon the Child!

And it may be hoped, with the more of Efficacy, because his dearest Companion (and his Chamber-fellow at the Colledge) dies this Day, of the Small-pox taken in the common Way.

The opponents of inoculation now found a newspaper devoted to their interests. This was the *New England Courant*, published and sold by James Franklin, which first appeared on the 17th of August, 1721. The *News-Letter* of Aug. 21-28, 1721, No. 917, contains a communication to its author signed by "*Your Friends and Well Wishers to Our Country and all Good Men.*" In it the Courant is characterized as

Notorious, Scandalous, full freighted with Nonsense, Unmannerliness, Railery, Prophaneness, Immorality, Arrogancy, Calumnies, Lyes, Contradictions and what not, all tending to Quarrels and Divisions and to Debauch and Corrupt the Minds and Manners of New England. And what likewise troubles us is, That it goes Currant among the People, that the Practitioners of Physick in Boston, who exert themselves in discovering the Evil of Inoculation and its Tendencies (several of whom we know to be Gentlemen by Birth, Learning, Education, Probity and good Manners that abhors any ill Action) are said, esteem'd and reputed to be the Authors of that Flagicious and wicked paper.

James Franklin, the editor and printer, soon came to grief, however, through his published criticisms of the government and was imprisoned. Zabdiel Boylston certified [35] to his illness while in the jail and Benjamin Franklin, nominally, continued the publication of the paper.

Despite the opposition of Dr. Douglass and most, if not all, of the practitioners and of the town authorities, inoculation was continued. Dr. Boylston was supported in his action by the leading clergymen of the town who wrote articles and pamphlets, "tracts" in its favor. Some of them saw his patients and advised their parishioners to undergo the operation and were themselves inoculated. Six of his own children, his brother and his sister-in-law were thus treated.

The General Assembly now transferred its place of meeting to the George Tavern at the outskirts of the town near Roxbury, and, August 26, 1721, stationed guards at the doorway to prevent the entrance of any but authorized persons from the infected region.[36]

According to Cotton Mather:[37] "The Town has become almost an Hell upon Earth, a City full of Lies, and Murders, and Blasphemies, as far as Wishes and Speeches can render it so; Satan seems to take a strange Possession of it in the epidemic Rage, against that notable and powerful and Successful way of saving the Lives of People from the Dangers of the *Small-Pox.*"

As the epidemic increased in severity so did the number of those inoculated. The better educated and more intelligent were in favor of the method, but the people at large were in violent opposition and objected to the advice of the ministers. In the *Gazette* of October 23-30, 1721, No. 101, there appeared what may be regarded as a report of progress by one, evidently Dr. Boylston, familiar with the conditions.

I. The Operation within these four Months past has been undergone by more than Three score Persons, Among which there have been *Old & Young; Strong* and *Weak; Male* and *Female; White & Black;* Many *serious* and *vertuous* People; some the Children of Eminent Persons among us. II. . . . . Only One Gentlewoman so circumstanced died; But her nearest Friends and all that knew her Case, do firmly believe the *Transplantation* was not the least occasion of it. *Of the rest, the following Account.* III. Of all the Number that have passed under the Operation, there has *Not so much as One miscarried.* It has done well *in all:* and even beyond Expectation in the most of them. IV. Some few have had a considerable Number of Pustules . . . . V. But the most by far, have endured in a manner *nothing.* Their *Pustules,* have been very few. From the time of the *Incision* to the time of their *Decumbiture,* (six or seven days) they have gone about their Business as at other times. After they began, and when they felt the Eruption coming on, they Satt up, and Read and Walk'd; and would have yet more expos'd themselves, if the Physician had not confined them. And they got abroad again sooner than what is ordinary for the Infected in the *Common Way* . . . . VII. The Patients return to their *perfect Health immediately;* and suppose themselves rather better than they were before the Operation . . . . VIII. Some of them have had nothing but a *Cabbage-Leaf* from first to last applied unto them. IX. Some, of whom the People have confidently affirmed *That they died under the Inoculation,* have sent their dying Charges unto their Friends, *To hasten into it.* These friends have done it; and so found their Account in it, and seen such *Easy Circumstances,* that the surviving Relatives of the Deceased are drowned in Tears, to think how the *Lives of Theirs* have been thrown away.

Nevertheless, the leaders in the opposition to inoculation continued to seek by legislation what the terrorizing of the mob could not effect. Apparently there was doubt whether protective measures against smallpox could be carried so far as to exclude inoculation. According to an Act in the time of William III the selectmen were empowered to remove patients with smallpox and place them in a special house. This had been established at Spectacle Island. Consequently, a town meeting was held November 4, 1721, and it was

Voted [38] that whosoever shal come into this Town of Boston from any other Town Presumpteously, to bring the Smal Pox on him or her selfe, or be Inoculated, Shal be forthwith Sent to the Hospital or pest house, unles they See cause to depart to their own home, or if any Person be found in Town under that operation, which may be an Occasion of Continuing a malignant Infection, and Increasing it, among us, that they be Remoued Immediately Least by alowing this practis the Town be made an Hospital for that which may prove worse than the Smal pox, which has already put So many into Mourning, And that the Justices and Select men be desired to put the Method abouesaid in practis, without Delay as the Law Directs.

[35] Province Laws, 1722, X, 174.
[36] Province Laws, 1721, X, 105.
[37] MS. Diary, Aug. 24.
[38] Town Records, 1721, 159.

The Selectmen took early action, as it is recorded [39] November 13, 1721, that

being Credably Informed that divers Persons belongin to other Towns are already come into this Town, and haue taken the Infection of the Smal pox, in the way of Inocculation, but that as yet the Infection has not Operated upon them yet Expect that in a few dayes it will, and that Divers others belonging to Other Towns, Intend to Come to this Town for the Purpose aforesaid, and that they know how to come in and where, and what Houses to use in Spite of the Town. And the Remoueing the Said Persons by Law being Impracticable but by Warrant from Some of his Majesties Justies of the Peace.

The Said Select men Therefore doe hereby give notice to the Justices of this Town of the afore said Practice and pray that they will Isue forth their Warrants to search for such persons as have or are to come for such purposes and remove them to their respective houses or to the province hospital.

Cotton Mather, however, though noting in his diary, November 3, 1721, the "Malicious and Murderous Manner" of the treatment received by him and despite, November 9, 1721, "the Sottish Errors, and cursed Clamours, that fill the Town and Country, raging against the astonishing Success of the *Small-Pox* Inoculated;" takes into his house his nephew, Mr. Walter, of Roxbury, for the purpose of being inoculated. While the latter was lying sick in his room, November 14, 1721, a lighted grenade intended for his host was thrown through the window, but the fuse became detached and burned itself out. On a paper attached to the fuse, according to the advertisement of Cotton Mather in the *News-Letter*, November 13-20, 1721, No. 929, were the words: "COTTON MATHER, *I was once one of your Meeting;* But the *Cursed Lye you* told of ..... You know who; *made me leave* You, You Dog, And *Damn* You, I will Enoculate you *with this, with a Pox to You.*"

In Cotton Mather's diary [40] it is stated that "the *Granado* was charged, the upper part with dried Powder, the lower Part with a Mixture of Oil of Turpentine and Powder and what else I know not," and the sentence referring to the lie is not included. Hutchinson [41] who saw the grenade states that it did not contain powder but was filled with brimstone and bitumen. Although most writers in referring to this incident assume that the violence was due to Cotton Mather's efforts in favor of inoculation, the phrasing of the note in the "advertisement" suggests that the grievance was more specific and personal. Cotton Mather, however, writes: [42] "The Opposition to it has been carried on with senseless Ignorance and raging Wickedness. But the growing Triumphs of Truth over it throw a possessed people into a Fury, which will probably cost me my Life. I have Proofs, that there are people who Approve and Applaud the Action of Tuesday Morning: and who give out Words, that tho' the First Blow miscarried, there will quickly come Another that Shall doe the Business more effectually." He considers [43] himself as "Being in daily Hazard of Death from a Bloody People." It is possible that this incident of the grenade is the source of the previously mentioned statement that one was thrown into Dr. Boylston's house.

The report of progress above mentioned was followed in the course of a month by the communication of the Reverend Benjamin Colman [44] to the same effect. He visited the sick and saw that

they *found ease* and *sweetness* and lay *praising* God on their *Beds* or rather sat up in their Chairs doing so. Their friends stood smiling about them. Their tongues were filled with laughter and ours with Thanksgiving on their account when we went to see 'em .... We saw *scores* thus recover, even as many as went into the happy practice .... They were as discreet and religious a number of People, and Persons of as good sense and understanding, and of as much caution and fear as their Nei'bors, who made these Experiments; and they did it with meekness and humility, patience and silence, and many prayers, under much provocation from too many .....

The distemper was now extended to Cambridge and Dr. Boylston inoculated a number of the students and two of the instructors. The General Assembly had been sitting in Cambridge since November 7, 1721, having been adjourned to this town on account of the epidemic in Boston, and Governor Shute, therefore, had asked for a short session. In the course of a few weeks, however, one of the Boston members died of smallpox. It was supposed that he had become infected through the Speaker, Dr. Clark, who was the leading physician of Boston and in active practice. The Assembly immediately adjourned and did not meet again until the following spring when the epidemic had ceased.

The custom of inoculating, urged as a duty by the leading citizens, ministers and magistrates, who offered examples in themselves and in their families, now became definitely established and ceased only with the disappearance of the disease.

During its course Dr. Boylston had inoculated 244 persons, and Dr. Thompson had inoculated 25 in Cambridge and Dr. Roby 11 in Roxbury. Dr. Boylston had inoculated 10 patients in Charlestown, but was so busy in Boston and Roxbury that he could see them but once. The *Courant* states: [45] "We hear 104 Persons have had the Small Pox inoculated upon them at Roxbury." Of the 280 inoculated persons only six died, a mortality of one in forty-six, in contrast to one in six or seven of those who had become diseased through contagion.

Reports now were received from London of the introduction of inoculation into England. The *News-Letter* of October 16-23, 1721, published as news from London that

A Representation has been made to his Majesty, by some Physicians, that the Small-pox may be communicated, and with great Success, by Incision or Inoculating, as 'tis commonly term'd, as might be experienc'd, if some proper Objects to practice on were found out. And we are assured that two of the condemned Prisoners, now in Newgate, have offered themselves to undergo the Experiment, upon Condition of receiving his Majesty's most gracious Pardon.

In the *Gazette* of October 23-30, 1721, it was announced that the eruption had appeared on some of the inoculated prisoners.

[39] Selectmen's Minutes, 1721, 90.
[40] MS. Diary, 14 Nov., 1721.
[41] Op. cit., II, 249.
[42] MS. Diary, 19 Nov., 1721.
[43] MS. Diary, 24 Nov., 1721.
[44] Some *Observations on The New Method*, etc., op. cit., 3.
[45] *Courant*, Dec. 5-Jan 1, 1721-2, No. 22.

The effect of these experiments is made apparent by the following quotation[46] from the *London Mercury* of September 16, 1721: "Great Numbers of Persons in the City and in the Suburbs are under the Inoculation of the Small Pox. Among the rest the oldest Son of a Noble Duke in Hanover Square."

Increase Mather published[47] an account of the communication of Dr. Walter Harris of London with regard to the inoculation of small-pox. In this is an abstract of the communication of Timoni and a statement of the inoculation of the children of the Hon. Wortley Montague. The *News-Letter* of March 5-12, 1722, No. 945, reports from the *St. James's Evening Post,* August 17, 1721, the letters of Timoni and of Pylarini as printed in the Philosophical Transactions and which Dr. Douglass had refused to show even to the Lieutenant Governor after they had been returned by Cotton Mather. Mr. Campbell, the publisher of the *News-Letter,* adds a note to the effect that a copy of these letters had been in his possession for five months.

The epidemic had now come to an end and Dr. Boylston's efforts met with a deserved recognition from Isaac Greenwood, afterwards Professor of Natural Philosophy in Harvard College. He published, February 25, 1721, 2, a pamphlet entitled, "A Friendly Debate; or a DIALOGUE between ACADEMICUS and SAWNY & MUNDUNGUS, Two Eminent PHYSICIANS, about Some of their Late PERFORMANCES." This he dedicated as follows:

To my very Worthy Physician, Mr. ZABDIEL BOYLSTON.

Sir,

I know no Person so proper, to present the following Dialogue to as your Self.

Such has been your undaunted Resolution, and truly Heroic Courage, thro' the whole Course of your dangerous Enterprize; and such Your Conduct and Wisdom, as merit our highest Regards, and most public Thanks. To *You* under the Auspicious Providence of GOD, we are Indebted for the Blessing of INOCULATION; for you can claim the undivided Honour of Introducing it among us. And hadst not thou began it, perhaps, there would not have been found a Soul so truly great, as to have undertaken it. For this, Sir, I am bold to say, Your Name shall be mention'd with Honour, whilst those Physicians, and others, who have signaliz'd themselves by their Malice and opposition to you, shall be otherwise spoken of.

Isolated cases still occurred and the Selectmen found it expedient to make the following proclamation,[48]

14 April, 1722: WHEREAS *sundry Evil-minded Persons have of late Industriously reported in the Country Towns, that the Small Pox is again very brief in this Town, many Persons now Sick of that Distemper, and sevcral lately dead. This is to Certifie that the Report is false & groundless, there being but three Folks now known to have the Small-Pox; . . . . Could the Inventor of such pernicious Lyes be fully discovered it would be of Publick Service. If any Families that have had that Distemper have not alrcady aired their Houscs and Bedding. It is Recommended to all such more especially Innholders and those that entertain Lodgers, that they would speedily take all proper carc, in well airing and clcansing their Houscs and Bcdding.*

On May 11, 1722, however, Dr. Boylston inoculated six persons and on May 15, 1722, it was voted[49]

that a gard be forthwith Set at the House of Mr Joseph Hubbard, Blacksmith to prevent the Removal of Mr Samll Sewal and Sundry others at Said House without orders and Direction of of the Select men they having bin Inoculated for the Smal Pox.

Voted also that there be a gard Set at the House of Coll John Alford for the Same Reason Mrs Joana Alford being there and having Inoculated.

* * * * * * * * * *

Voted that a message be sent to Coll John Alford (by Doctr Boylston & Constable Titmarsh) to acquaint him that the Select men Doe Assigne Spectakle Island to be [the] place his Sister be forthwith Remoued unto.

At the same meeting a committee was appointed[50] to draw up instructions for the representatives of Boston to present to the Assembly for the purpose of preventing the practice of inoculation in any town or place without the approval of the Selectmen. This vote was passed because there had been dispute whether the law relating to the spreading of smallpox gave full power to the Selectmen to do what was needful to prevent the spreading of any contagious distemper and remove persons who may be infected.

On the same day the Selectmen applied[51] for a warrant to remove Mr. Sewall, his wife, two children and one other of his family who had been inoculated from Mr. Hubbard's house to Spectacle Island, also to remove Joan Alford.

The committee appointed at the town meeting of May 15, 1722, reported[52] three days later:

We also in a Special manner Recomend to your Consideration what Refers to the preventing the Spreading of any Contagious Distemper And whereas the Inoculating or Transplanting of the Smal pox has of late bin practised among us to the Terror of many of the Inhabitants.

We desire you to use your best Endeavor that it may be under a propper Regulation, and not practissed in any Town or place without the approbation of the Select men of Such Town, And in as much as there has bin some late Dispute about the meaning of the Law that Refers to preventing the spreading of the Smal pox, etc., whether the Select men have full power to doe what is needfull to prevent the Spreading of any Contagious distemper and Remoue persons that may be Infected. It is therefore proposed that the Select men of Every Town may be Clothed with full power to obtain the great End & Designe of that Law, which is for the Preservation, Health and Safety, of the Inhabitants.

In the *Courant* of May 14-21, 1722, No. 42, the following notice is inserted:

By the Select-Men of Boston

Whereas it is reported in the Country Towns, That great Numbers are now sick of the Small Pox in Boston, not only in the Common Way, but also that greater Numbers are inoculated for that Distemper, These are therefore to signify That the said Report is false and groundless; for that according to the best

[46] *Courant,* Dec. 25-Jan. 1, 1721 (2), No. 22.

[47] Gazette, Jan. 29-Feb. 5, 1721 (2), No. 115; also, Some further Account from *London* of the *Small-Pox Inoculated.* The Second Edition, 1721 (2).

[48] News-Letter, April 9-16, 1722, No. 950.

[49] Boston Town Records, 1722, 165.

[50] Boston Town Records, 1722, 165.

[51] Selectmen's Minutes, 1722, 97.

[52] Boston Town Records, 1722, 166.

Informations, there are not above three or four now sick in the Town in the Common way; and the Select Men having sent for Dr. Boylstone, he solemnly declared in the publick Town-Meeting, that there were no more than six Persons in Boston under Inoculation of the Small-Pox, and that it was performed on them on *Friday* and *Saturday*, the 11th and 12th Instant; And the said Doctor Boylstone then also did solemnly declare and promise That he would not either directly or indirectly inoculate any Person within said Town for the Future *without License* and Approbation of the Authority of the Town.

Whereupon they may also certify, That the said Six Persons under Inoculation, were by Order of said Select Men, and Warrant from Two Justices of the Peace, immediately sent down to the Hospital on Spectacle Island.

According to Hutchinson,[53] the Representatives passed a bill prohibiting inoculation, but the Council refused to agree to it. It took special action, however, with reference to the inoculated persons at Spectacle Island by ordering,[54]

2 June, 1722. That the persons so Inoculated shall not Come up to the Town of Boston during this present Session of the General Assembly without Leave first obtained.

The simultaneous introduction of inoculation in England, although meeting with decided opposition, was not attended with such excitement and fear as in Boston. At this time Sir Hans Sloane was one of the most distinguished physicians in London. He was President of the Royal College of Physicians, Physician-General to the Army, one of the physicians to Queen Anne and present in her fatal illness. He was also the physician of the Princess Caroline, wife of George II. He had been Secretary to the Royal Society, and it was at his instigation that Pylarini had written the account of inoculation published in the Philosophical Transactions in 1716.

His participation in the introduction of inoculation into England led him to prepare a statement which he intended should be published in 1736, although it was not printed until some twenty years later.[55]

It appears that the Princess Caroline had become interested in the subject on account of the dangerous illness of her daughter whom Dr. Sloane was treating for smallpox, and doubtless had been made acquainted with the communications in the Philosophical Transactions. She knew of the successful inoculation of the Montague children and requested that the experiment might be tried upon some condemned criminals who were to be freed in case of its success. This was done by Mr. Maitland, the surgeon who had inoculated the Montague children. In order to test the protective influence of the inoculation Sir Hans Sloane and Dr. Steigerthal, physician to George I, hired one of the inoculated criminals to act as nurse and bedfellow to a patient with smallpox. Princess Caroline also caused several charity children to be inoculated. The success of these inoculations and of others led the princess to ask Dr. Sloane for his opinion of the expediency of inoculating her daughters. Through his statements to her and to George I, two of her daughters were inoculated,[56] April 19, 1722, by Sergeant-Surgeon Amyand under the direction of Sir Hans Sloane. Two years later two of her sons were inoculated, one in Germany by Mr. Maitland, the other in London by Sergeant-Surgeon Amyand, again under the direction of Sir Hans Sloane.

The progress of inoculation during the epidemic in Boston had been followed in England. The Reverend Mr. Mather sent a statement,[57] dated March 10, 1722, showing the mortality of inoculated smallpox to have been only one in sixty, although at a later period in England there were but two deaths in 182 cases. This contrast led Dr. Jurin, then Secretary of the Royal Society, to consider that the operators in England were more cautious. That this was not the universal opinion appears in an extract from the letter of Dr. Thomas Robie written from Salem, June 4, 1723. In this he states:[58]

We don't as yet See any ill Effects of Inoculation, but the Inoculated are as yet as well, and some of them a great deal better than ever; as for the ill Consequences that have been in England, I can't tell what they may arise from, but I can hardly think they are the genuine effects of Inoculation, but may arise from some previous Disposition to such Distempers as you mention or for want of due Evacuation after Inoculating and too soon healing the places of Incision.

With the diminution in the mortality from smallpox in England came a lessening in the frequency of inoculation, but in 1725 the number of deaths from smallpox in London was 3188, one-eighth of the total mortality,[59] although during this year only 151 persons were inoculated in Great Britain and only 105 persons in the following year.

It was at this time that Zabdiel Boylston spent a year in England. He was then the inoculator with the largest individual experience, although his publications on the subject were but few and brief. It is quite possible that he had been invited to visit England for the purpose of presenting this experience, especially as he had made no further communication since the cessation of the Boston epidemic in 1722. Douglass[60] suggests that he went to England to seek profitable employment as an experienced inoculator on account of lack of business at home. This slur was immediately answered[61] in a communication dated March 3, 1729, 30, in which it is stated that Dr. Boylston, though often asked, refused to inoculate persons while in London.

It is quite probable that Sir Hans Sloane invited him to visit London, certainly he urged him to publish his experience. The latter is made apparent in his preface to the "Historical Account." In this he declares that

Writing is a Talent which, of all Things, I never made any Pretentions to and little thought of giving at this Time the

[53] Op. cit., II, 249.

[54] Province Laws, X, 161.

[55] Phil. Trans., 1755, XLIX, 516.

[56] The *History* of the *Inoculation* of the *Small-Pox* in *Great Britain*, etc. William Woodville, 1796, I, 104.

[57] Phil. Trans., XXXII, 1724, 213.

[58] Phil. Trans., XXXIII, 1726.

[59] Woodville, op. cit., 175.

[60] Dissertation Concerning Inoculation of the Small-Pox, 1730.

[61] A Letter to Doctor Zabdiel Boylston; Occasioned by a late Dissertation Concerning Inoculation; Printed at Boston, MDCCXXX.

Publick an Account of my Practice; but being again importuned thereto, by a great and worthy Physician, and having also receiv'd a Message from a Superior Person that an Account of my Success of inoculating the Small-Pox in New England might be grateful, as being of great use, and beneficial to the Publick, I esteem'd it as the strongest Obligation upon me so to do, and in Compliance to that Command I have done it faithfully. If I had proposed any Advantage to myself, in the Practice here, I should have done it above a Year past, on my Arrival in London, and not now on my return home.

It is surmised that Dr. Boylston first presented his experience to the Royal College of Physicians of which Dr. Sloane was President, or to the Royal Society of which he was made a member in July, 1726, but direct evidence upon this point is lacking. The only published [62] communication made by him to the latter is on "Ambergris in Whales," reference to which and to his love for horses is to be found in a MS. letter in the Massachusetts Historical Society from him to Benjamin Colman, dated London, February 26, 1724, 5.

The "Historical Account" is printed in almost a sumptuous manner as compared with the second edition published in Boston in 1730. Its form suggests that Dr. Boylston's affairs were in a prosperous condition at the time, and additional evidence on this point, as well as of a kindly if not forgiving disposition, is afforded by Ward Nicholas Boylston's statement [63] of his interview with Benjamin Franklin. While near Paris in 1783, Mr. Boylston was introduced to Franklin who said to him,

"I shall ever revere the name of Boylston; Sir, are you of the family of Dr. Zabdiel Boylston of Boston?" to which I replied that he was my great-uncle, "then, Sir, I must tell you I owe everything I now am to him. . . . . When Dr. Boylston was in England, I was there reduced to the greatest distress, a youth without money, friends or counsel. I applied in my extreme distress to him, who supplied me with twenty guineas; and relying on his judgment, I visited him as opportunities offered, and by his fatherly counsels and encouragements I was saved from the abyss of destruction which awaited me, and my future fortune was based upon his parental advice and timely assistance. Sir, I beg you will visit me as often as you find you have leisure while in Paris."

Little remains to be recorded of Dr. Boylston's career subsequent to his return to Boston, which he reached before the end of October, 1726. He resumed his practice, which must have been greatly in demand after his reception in England. Indeed it is called [64] "great in town and country" and "every Practitioner gives him the preference to Douglass in curing disease." The practice of inoculation had become so well established that in the epidemic of 1729-30, imported from Ireland, the Selectmen no longer were urged to remove the inoculated to the pesthouse, but precautions were recommended to protect the inhabitants from those inoculated within the town. The following extract [65] from the Town Records illustrates this change of sentiment. At the town-meeting of March 10, 1729, a petition was presented by some of the inhabitants

That the Town might Consult proper methods for preventing the spreading of the Small Pox by Inoculation.

Since the Date of which Petition a Considerable Number of the Inhabitants within a few days past have bin Inoculated, and Sundry Others are preparing therefore, In Consideration whereof the Town came unto the Following Vote,

That it be Earnestly Recommended to the Inhabitants and Freeholders and in an Especial Manner to Masters of Familyes. That all Proper care be taken That Such Persons as Shall for the Future be Inoculated for the Small Pox do Imediately keep in their Houses First giving notice to the Neighborhood of Such their Designs, And that during the Opperation of the Distemper all proper Methods be taken to prevent it's Spreading. And that they would not come or walke abroad in the Streets, Lanes or Alleys within the Town Until their Incisions are well clensed and Healed: Further that the Practitioners in Physick would give to the Select men or to the Town Clerk, the number of Persons by them Inoculated once a week at least, with an Impartial Account of the Operation on their Several Patients in the Course of their Inoculation.

Of the physicians who originally had opposed inoculation, Dr. Williams [66] entered upon its practice in 1730 "with the utmost caution." Dr. Cutler [67] writes to Dr. Gray of London, May 30 (1730?):

The Small Pox is now overspreading this town and strikes terror into the whole country. The Contagion has proved mortal to many, and has therefore inclined great numbers to venture upon inoculation, which has been attended with great success. I have submitted my wife and seven children and a servant to the practice. The most visible effect of this affliction is to *set us in parties*. The main of the church are against it; and it seems that he is no Churchman or Christian who is for it.

Even Dr. Douglass [68] regarded it as "a considerable improvement in Physick." He states that most of those opposed acknowledge that inoculated smallpox is easier than when the disease is accidentally received, that the former is less fatal and that the symptoms are more favorable. He finds that it is the custom for the practitioners to inoculate when requested, but not to persuade or dissuade the applicant. In the last years of his life he became a more earnest advocate and recognized [69] that

The novel practice of procuring the Small-pox by inoculation, is a very considerable and most beneficial improvement in that article of medical practice . . . . The small-pox received by cuticular incisions has a better chance for life and an easy decumbiture; that is, the small-pox so received is less mortal and generally more favourable, than when received in the accidental or natural way.

[62] Phil. Trans., 1726, XXXIII, 193.
[63] N. E. Hist. & Genealog. Reg., 1881, XXXV, 150.
[64] A *Letter* to Doctor *Zabdiel Boylston*, etc., 1730.
[65] Boston Town Records, 1729, 14.
[66] The METHOD of Practice in the SMALL POX with Observations on the Way of Inoculation. Taken from a Manuscript of the late Dr. Nathaniel Williams, etc. Edited by Thomas Prince, MDCCLII, 13.
[67] A Brief Memoir of William Douglass, M. D. By Timothy L. Jennison, M. D., Mass. Med. Soc. Comm., 1834, V, 236.
[68] Dissertation Concerning Inoculation of the Small Pox, MDCCXXXI, 8.
[69] *A Summary*, etc., op. cit., II, 406.

He continues[70] to credit Cotton Mather with no other motive than "the desire for the *imaginary honour* of a new-fangled notion," and his sentiments towards Dr. Boylston remain unchanged. For he adds in a foot note,[71] "This undaunted operator imagined that by going to London with a quackbill of his inoculation performance in New-England, he might acquire a fortune in London; but so it happened, that void of common discretion to couch his ignorance and silly mean assurance, he returned to Boston without being called upon to perform any inoculation."

By way of contrast his friend, Dr. Isaac Watts, writes to Dr. Boylston from Newington in a letter of April 25, 1735, reproduced by Peter Thacher[72] in his memoir, "The inoculation was a glorious and successful retreat, or if you will, a victory over the powers of death in Boston, when it was first practised under your conduct. It has not been so happy among us in England, nor do I find it has been equally happy in New-England since, but the want of conduct in the undertakers, may be are considerable cause of it."

After the publication of the American edition of Bolyston's Historical Account, in 1730, there was no further epidemic of smallpox in Boston until 1752. Douglass relates[73] that

> A ship from London, Capt. Cousins, with the small-pox aboard, was bulged Dec. 24, 1751, in Nahant bay near Boston; the people of Chelsey, the adjacent town, compassionately assisting to save the ship's crew, received the small-pox; about one in four or five died. . . . . It arrived in Boston in January following, by a sailor belonging to the Ship, and got into five or six families, but did not much spread till the twentieth of March, 1752, and Monday the twenty-third, inoculation was let loose; some greedy practitioners indiscriminately inoculated any persons who could be pursuaded to receive it, even pregnant women, puerpeas, old negroes, and the like.

Of the 15,734 residents of the town 1800 fled through fear of the smallpox; of those remaining 7,653 had smallpox; of these 2109 were inoculated.[74] The mortality among those not inoculated was one in ten or eleven, while of the inoculated only one in sixty-eight died. In England under Daniel Sutton and his assistants, between the years 1764 and 1766, nearly 20,000 persons were inoculated with but three deaths and these were not fairly attributable to the inoculation.[75]

Dr. Boylston thus lived long enough to see inoculation well-established and successful and to know that he was recognized as one of the world's benefactors.

Dr. Thomas Boylston, the father of Zabdiel, owned a homestead of ninety-six acres in Brookline which after his death was deeded and sold to Peter Boylston by his brothers and sister. About the year 1736, Dr. Zabdiel Boylston, who is said to have accumulated a handsome fortune, bought the homestead of his brother Peter, who removed to Boston and opened a shop.[76] After purchasing the homestead, he built the mansion still standing in excellent preservation and now the residence of Mr. George Lee. In 1741 his brother Peter's pew was transferred to him, and in 1744 he voted at a town meeting in Brookline. It is known that he continued to practise medicine until he was over seventy years of age, for among the MSS. of the Boston Public Library is a certificate which Zabdiel Boylston of Boston gave to Thomas Fleet in November, 1752, to the effect that the physical disability of the latter was such as to prevent his being exposed as a watchman in bad weather. This library also possesses a receipt from him for medicines and attendance dated Boston, April 23, 1753. It is probable that Dr. Boylston resided continuously or interruptedly in Brookline during this period, but eventually he retired to his country seat where, according to Peter Thacher, "enfeebled by age and disease he passed his last days in the dignity which ever accompanies those who have acted their part well in life."

Inscribed on his tomb in the old cemetery at Brookline, not far from his boyhood's home, are the words:

> Sacred to the memory of Dr. Zabdiel Boylston, Esq., physician and F. R. S. who first introduced the practice of inoculation into America. Through a life of extensive benevolence, he was always faithful to his word, just in his dealings, affable in his manners, and after a long sickness, in which he was exemplary for his patience and resignation to his Maker, he quitted this mortal life in a just expectation of a happy immortality, March 1, 1766.

The following is the text of the manuscript letter of the Reverend Benjamin Colman in the possession of the Boston Medical Library which seems to have served as the original of that published in the *Boston Gazette* of July 27, 1721, and signed by Increase Mather, Cotton Mather, Benjamin Colman, Thomas Prince, John Webb and William Cooper.

To the Reverend Mr..... of *Boston.*

Sir, It was a pleasure to me yesterday to hear you express the Sense you have of the unworthy Treatment which Dr. *Boylston* has received this week in the *Boston News-Letter.* The angry & contemptuous Letter there is below the Learning & Worth of the *Gentleman* who is said to write it. It breathes nothing of that native Modesty & Meekness which adorns Dr. *Douglass*, nor discovers that purity of Style & Diction which one wd expect from his Erudition. Besides, He has met with so kind & cordial an Esteem in the Town, as were enof to subdue the heart of a rough & unpolished Stranger (the Reverse whereof he is) to ye most humane & placid treatment of every body belonging to it. I Entirely dismiss ye tho't therefore that one of his Silence & Civility is capable of this sudden & angry Effort against a *Son* of the Town, whom Heaven (he knows & we all know) has adorn'd with some very peculiar Gifts for the Service of his country, & has signally own'd in the Success which he has had.

If Dr. *Boylston* was too suddenly giving into a new practice & dangerous Experiment & and also was too confidant of the Innocence & Safety of ye Method & of the benefit wch the Public would reap thereby; altho' in that case we are highly obliged to any learned & judicious Person who kindly informs us of the hazard & warns against the Practice; yet what need is there any injurious words, or mean detracting from the known worth of the

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[70] *Summary*, etc., II, p. 409.
[71] *Summary*, etc., p. 409.
[72] Loc. cit.
[73] *Summary*, etc., II, 347.
[74] Selectmen's Minutes, 1752, 283.
[75] The Practice of Inoculation Justified, A Sermon by Robert Houlton, M. A., Chaplain to the Earl of Dorchester and officiating Clergyman of Mr. Sutton's. Essex, 3d Ed., 1767.
[76] Selectmen's Minutes, July 7, 1737.

Doctor? Especially how worthy & unjust (to say no worse) is it to attempt to turn *that* to his reproach which has been & is a singular honour to him & felicity to his Country? I mean those words in the Letter—*a certain Cutter for the Stone.* Yes, thanks be to God that we have such a *One* among us, & that so many poor Miserables have already found the benefit of his gentle & Dextrous Hand. We that have stood by & seen his tenderness, courage & skill in that hazardous Operation cannot enof value ye Man & give praise to God. And I could easily speak of other Cases of equal hazard, wherein the Doctor has served with such Successes, as must render him Inestimable to them yt. have been snatch'd from the jaws of Death by his happy hand.

I blame the Letter for gross *partiality* wch treats Dr. *Boylston* with so severe a Surmise as to say, that he understood the matter of Inoculating *without a serious tho't;* when at ye same time it has the goodness to suppose of another *Doctor*, a *Divine* among us (who push'd on ye Attempt & openly rejoiced in it) that he acted *out of a pious & charitable design of doing good.* I verily believe Dr. *Mather* did so, & why should I not hope the same of Dr. *Boylston?* Is it that a Dr. in *Physic* or a Master in *Surgery* is not capable of the like pious & charitable design with a Dr. in *Divinity?* I am sure I ought to judge ye *best* of my Nei'bours, designs, & *who art thou to forget another?* Well, but this *Boylston is Illiterate*, says the Letter; that is to say, He has not had ye Advantages of a Liberal Education, which Dr. *Clark*, Dr. *Williams* & Dr. *Douglass* have had. He ought to vail to them therefore on that account & congratulate them their Advantage. But must he be therefore called *ignorant & quack?* as the Letter rudely calls him: Would ye Town bear that Dr. *Cutler* & Dr. *Davis* should be so treated? No more can it endure to see *Boylston* thus spit at.

The *Town* knows & so does ye *Country* how *long* & with what *Success* Dr. *Boylston* has practis'd both in *Physic* & *Surgery;* & tho' he has not ye *Letters* of some Physicians in the Town, yet he has been so happy as to have had more *practice* it may be than any one, Dr. *Clark* excepted: Nor has it been without considerable Study, expence in *Travel*, a good *Genius*, diligent application & a great deal of observation, that he has attain'd unto that knowledge & successful practice wch he has to give thanks unto God for; & wherein I pray God that he may improve & grow with all humility. Then he would not fear want of Business, nor I trust of Usefulness & Esteem: for there are but too many likely to need him, even in Cases wherein none beside him can as yet equally serve.

This I have said in Justice & friendship, as to Dr. *Boylston* & his numerous *Family* to whom I ought to wish well, as likewise unto *Others* among us who have gone into favourable opinion of *Inoculating the Smal pox*, among whom I acknowledge my self to be One: But if it be an *evil & dangerous Method*, as the other *Physicians* of ye Town (to whom we owe great honour & regard) have declared it to be in their Judgment, They have done well to warn the people ag't. running into it: & for my own part I now give the *Gentlemen* my Thanks for the *Resolve* which they have lately published for this end.

The meanwhile I heartily wish Men would treat one another with *decency & charity*, meekness & humility, as becomes fallible Creatures & hearty friends to one another & to their Country; that so our prayers may be more united in this Day of common distress to ye. God of our *Health*, who is ye. *God of love & peace.*

Postscript

As to the *Case of Conscience* referred to the *Divines* in the *Letter* wch I have been Animadverting on, I suppose there never was the like put before to *any.* Wt. *heathens* must they be to whom *this* can be a question. *Whether the trusting more the extra groundless Machinations of men than our Prescrver in the ordinary course of Nature, may be consistent with that Devotion & Subjection we owe to the Alwise Providence of God almighty,* who knows not the profanity & impiety of trusting in Men or Means more than in GOD; be they the most learned men, or ye most proper means? But I will suppose *Men of piety & learning* too, (for Instance Such as Dr. *Mather* & Mr. *Webb*, who are opposite *Names* in the present case) after much curious Tho't come into an opinion of the Safety of the saulted method of *Inoculating* the *Smal Pox;* & being persuaded yt. it may be a means of preserving a multitude of lives, they accept it with all Thankfulness & Joy as the gracious Discovery of a kind *Providence* to Mankind for that end; And then I ask—cannot they give into the method or practice without having *their Devotion & Subjection to ye all-wise Providence of GOD Almighty call'd in question?* Must they needs *trust more in men than in their* Great *Preserver* in the use of *this* means than in using other means? What wild kind of *Supposition* is this? Do we not in the use of any Means depend on GOD's blessing? & *live* by that alone? & can't a devout heart depend on GOD in the use of *this* means, with infinite gratitude, being in the full Esteem thereof? What hand or art of *Man* is there in this Operation, more than in bleeding, blistering, & a score more things in *Medical use*, which are all well consistent with a *humble Trust in our great Preserver, & a due Subjection to his all-wise Providence?*

Benjamin Colman.

Boston, July, 25, 1721.

HENRY NEWELL MARTIN,

*Professor of Biology in Johns Hopkins University, 1876-1893.**

By HENRY SEWALL, M. D., Denver, Col.

The name I wish to introduce to you is that of Henry Newell Martin, M. A., M. D., D. Se., F. R. S., Professor of Biology in Johns Hopkins University from its foundation in 1876 to the time of his resignation in 1893, a period of seventeen years. It may fairly be inquired why, with the exhaustless material at my disposal, I have settled on this one life for exposition. For Martin never for one moment was included by any who knew him within that eerie group possessing attributes we denominate "genius." He was simply an upright, high-minded man with human foibles; he had sound common sense and much tact at his disposal. He possessed no very extraordinary talent or learning. Trained under Sharpey and Huxley and Michael Foster, the truths of nature were the canons of his religion and this education was not only assimilated in the development of his own character but was through him an efficient epoch-making force in the scientific development of our country. It is, I think, worth while enquiring how a young man entering at the age of twenty-eight, without the foundation of experience, upon an academic position whose ideals from the outset departed radically from any that had been hitherto aimed at in the pedagogic history of America,

* Read before the Denver Medical-History Club, Feb. 16, 1911.

had, as I believe, come to deserve the foremost niche in the temple of American physiology which, I venture to hold, is the fountain head of American medicine. In 1876 there was no real profession of either physiology or pathology in the United States. Ambitious young medical graduates got their first hold on medical faculties by undertaking the instruction of students in the perfunctory study of the merely tolerated, if not despised, unpractical or "scientific" bases of clinical diagnosis and treatment—physiology and pathology. Splendid and brilliant men there were scattered about the country and associated with institutions of learning, medical and academic, but their pedagogic relations were limited to the teaching of students. In those days knowledge in America was chiefly founded on authority, not on individual research. True enough, certain original spirits, like Weir Mitchell, H. C. Wood, O. W. Holmes, the Bowditches and many others known to fame, broke through the restraints of convention and lifted here and there a torch to inflame the mind. But the prosecution of original research requires a devoted union of aggressiveness, patience, courage and self-denial which rarely thrives in isolation. It must be surmised that in those days and long preceding, countless pregnant thoughts had sprung up in fertile minds to bloom and fade and die without bearing fruit.

What the Johns Hopkins University did for science and what its Biological Departments did for Medicine was to offer a culture medium and an incubator for scientific ambitions and ideas. Here young men were invited to study and engage in original research under the direction of those who themselves were skilled investigators and amid the stimulating companionship of contemporaries whose talents had already marked them as leaders for the future.

The progress of biological science and art for the past quarter century in this country has sufficiently attested the extraordinary potential energy of the conceptions put in operation at the Johns Hopkins University in 1876. Today there is an American medical science which in my opinion has been made possible only through that massed play of endeavor which in another field Napoleon used to win his victories and a conception of which led Bismarck to make a nation out of futile single states. In short, to employ the vernacular, Newell Martin was the pioneer professional coach in scientific medical team work in America.

Let it be noted that I use the word "Medical" in its profound, most modern significance as that which indicates a conception of vital processes *per se* and which takes it altogether away from that narrow view whose vista was limited by a pill and bound on either side by a saw and an amputating knife. In Martin's time the leaders of thought in physiology felt themselves confronted with a calamity which endangered the autonomy of their science. Physiology in this country did not exist as a profession. Its reason for existence in the mind of even the educated public rested on its relation to medical instruction and it held somewhat the same position in the technical curriculum as grammar does in the academic course. Martin, following the lead of his scientific forebears, insisted that physiology should be regarded as the benefactor not the handmaid of Medicine and that it should be cultivated as a pure science absolutely independent of any so-called practical affiliation. Possibly this question has not yet burned itself out and certainly it is not expedient here to rake the embers, but I must vent the impression that the course of evolution has ordered it that whereas physiology was then the dependent runt of the medical family it is today the eldest son in a stable system of primogeniture. As with a noble jewel whose beauty depends upon the cutting, we may name one facet Pathology, another Pharmacology, another Bio-chemistry, another Psychology, and so on, the jewel itself remains and ever will be Physiology.

I will quote bodily from an obituary notice of Martin contributed by Sir Michael Foster to Volume 60 of the *Proceedings of the Royal Society*. It is as follows:

Henry Newell Martin was born on July 1, 1848, at Newry, County Down, Ireland. He was the eldest of a family of twelve, his father being at the time a Congregational minister, but afterwards becoming a schoolmaster. Both his parents were Irish, his father coming from the South of Ireland and his mother from the North. He received his early education chiefly at home, for though he went to several schools, his stay was not long at any one of them. Having matriculated at the University of London before he was fully sixteen years of age (an exemption as to age being made in his favor), he became apprentice to Dr. McDonagh, in the Hampstead Road, London, in the neighborhood of University College, on the understanding that the performance of the services which might be required of him as apprentice should not prevent his attending the teaching at the Medical School of the College and the practice in the Hospital. During his career at University College he greatly distinguished himself, taking several medals and prizes, in spite of his time for study being, on account of the above-mentioned duties, less than that of his fellow students. In 1870 he obtained a scholarship at Christ's College, Cambridge; he had in the summer of that year conducted at Cambridge a class of Histology for the late Sir G. Humphrey. The writer of this notice had at about the same time been appointed Prælector of Physiology at Trinity College, and the two went up to Cambridge together in the October of that year. He at once undertook to act as the demonstrator of the Trinity Prælector, whose right hand he continued to be in every way during the whole of his stay at Cambridge. His energy and talents, and especially his personal qualities, did much to advance and render popular the then growing School of Natural Science in the University.

At that time there was, perhaps, a tendency on the part of the undergraduate to depreciate natural and, especially, biological science and to regard it as something not quite academical. Martin by his bright ways won among his fellows sympathy for his line of study, and showed them, by entering into all their pursuits (he became, for instance, President of the Union and Captain of the Volunteers) that the Natural Science student was in no respect inferior to the others. In Cambridge, as in London, his career was distinguished. He gained the first place in the Natural Science Tripos in 1873, the second place being taken by Francis M. Balfour. At that time the position in the Tripos was determined by the aggregate of marks in all subjects. While at Cambridge he took the B. Sc., and M. B., London, gaining in the former the scholarship in Zoölogy. He proceeded later to the D. Sc., being the first to take that degree in Physiology. So soon as, or even before, he had taken his degree, he began to devote some time to research, though that time, owing to the necessity

under which he lay of making money by teaching, was limited. His first publication was a little paper on the Structure of the Olfactory Membrane which appeared in the Journal of Anatomy and Physiology for 1873. In the summer of 1874 he assisted the Trinity Prælector in introducing into Cambridge the course of elementary Biology, which the late Professor Huxley had initiated at the Royal College of Science during the preceding year. He subsequently acted as Assistant in the same course to Professor Huxley himself. One result of this was that he prepared, under Huxley's supervision, a text-book of the course, which under their names, appeared with the title Practical Biology and which has since been so largely used. In 1874 he was made Fellow of his College, and giving himself up with enthusiasm to the development of natural and especially of biologic science at the University, was looking forward to a Scientific career in England, if not at Cambridge. About that time, however, the Johns Hopkins University at Baltimore was being established, and such was the impression made by Martin upon those with whom he came in contact, among others, Dr. Gilman of Baltimore, that in 1876 he was invited to become the first occupant of the Chair of Biology which had been founded in the Johns Hopkins University.

Martin married in 1879 Mrs. Pegram, the widow of an officer in the Confederate Army, but there was no issue, and in 1892 his wife died. Even before his wife's death his health had begun to give way, and after that he became so increasingly unfitted for his duties, which his own previous exertions had raised to a very great importance, that in 1893 he resigned his post. After his resignation he returned to this country, for he had never become an American citizen, and was looking forward to being able, with improved health, to labor in physiological investigations, either at his old University or elsewhere in England. But it was not to be. Though he seemed at times to be improving, he had more than one severe attack of illness and never regained sufficient strength to set really to work. During the past summer he visibly failed, and while he was striving to recover his strength by a stay in the quiet dales of Yorkshire, a sudden hemorrhage carried him off on October 27, at Burley-in-Wharfedale, Yorkshire.

I do not fear to make my sketch redundant by quotation of other less formal words of the same writer. When in September, 1900, on his return journey after delivering the course of Lane lectures in San Francisco, Sir Michael Foster stopped for a few days in Denver, and the Medical Department of the University of Denver enjoyed the unique privilege of hearing from his own lips an extemporaneous and colloquial review of men and events as recalled from his own scientific career. I have ventured to insist at the outset of this narrative that the establishment of physiology as a profession in the United States was due chiefly to the stimulus given to physiological research and diffusion of physiological instruction by Professor Martin at the Johns Hopkins. And as Martin's knowledge, methods and inspiration were all developed in England it will be interesting to get a glimpse of the status of physiology in that country just antecedent to the time of which I write. To quote from Foster's Denver address:*

> Sharpey was the only man at that time (1850) who devoted his whole life to physiology. In all the other schools physiology was taught by practicing physicians and surgeons. . . . . Now Sharpey was at the time I am speaking of the greatest physiologist in England, the only person who devoted his whole time to science, and yet even he taught physiology entirely by lectures. He had no physiological laboratory. He had no physiological apparatus whatever. All he did in the way of practical teaching at that time was to show us under the microscope preparations of the various tissues. There was no attempt whatever at any practical teaching of physiology. I remember very well when he was lecturing on blood pressure, and was describing to us the then new results of Ludwig, endeavoring to explain to us the blood pressure curve, all he had to help him was his cylinder hat, which he put upon the lecture table before him and with his finger traced upon the hat the course of the curve. That was the way that physiology was taught by Sharpey in England in 1854. . . . . Nobody else in England then was teaching physiology as Sharpey taught it and, as I tell you, he used his hat, and a very old hat it was, as a kymographion for blood pressure. I very well remember going to him one day after his lecture, in which he had been speaking of the functions of the liver (by that time he had recognized that I had a special interest in physiology), and he said to me: "Well," he said, "I didn't like to say anything about it in my lecture, but Claude Bernard in Paris has just sent me a paper which he has read before the Academy of Sciences at Paris and in that paper he has proved that there is present in the liver a substance resembling starch, which is easily converted into sugar."

Foster then stated that, having taken his qualifications, he practiced medicine in the country for six years but was then called back to London to teach practical physiology in University College where a subordinate lectureship in that subject had been established under the influence of Sharpey.

> That was in the early sixties, in about sixty-four or sixty-five. But what could be done then was very, very little. I had a very small room. I had a few microscopes. But I began to carry out the instruction in a more systematic manner than had been done before. For instance, I made the men prepare the tissues for themselves. That was a new thing in histology. And I also made them do for themselves simple experiments on muscles and nerves and other tissues on live animals. That, I may say, was the beginning of the teaching of practical physiology in England. . . . . These lectures on physiology were absolutely voluntary, and only the better students were willing to give up the time needed to get a more thorough grasp of physiology. Well, I appointed a time to see the few who wished to spend some time in this new study, this study of luxury, and there came to me a boy nothing more than a boy, who said: "I am very sorry, sir; I should like to take your course if I could, but you see my parents are not very well off, and I get my board and lodging by living with a doctor close by. . . . . I have, in return for my board, to dispense all the doctor's medicines, and that dispensing takes me from two to five; now your lectures begin at four. I cannot come for the first hour; I will work hard and will try to make up the lost time." I said "certainly, certainly." So he came in, came in regularly late. He came in regularly at five o'clock, and he worked with such purpose that in the examination which I had at the end of the course I awarded him the prize. Well, his name was Henry Newell Martin, and I was so much struck with him that I asked him to assist me in my course, and he became my demonstrator. After we had been at University College together I think two or three years, Martin carrying on his studies and at the same time helping me, he came one day to me in great trouble because he could not make up his mind. He obtained what they call a scholarship at Christ College at Cambridge and he could not make up his mind to accept it and go there. He said he didn't want to leave me. But I was able to tell him what nobody else knew at that time, that in the October in which his scholarship would take him to

* *Vid. Colorado Medical Journal*, Oct., 1900.

Cambridge I was going to Cambridge too, having been invited to lecture there. . . . And after a career of considerable brilliancy of some years at Cambridge there came to him an invitation to the Johns Hopkins University at Baltimore. So if I have done nothing more, at all events I sent Henry Newell Martin to America.

It was one of those chances which determine the course of human life by which it happened that the writer of this article, a native of Baltimore, graduated at the age of twenty-one from a New England College some three months before the inauguration of Johns Hopkins University. Through the kindly offices of that sweet and gentle character, Dr. James Carey Thomas, a member of the original Board of Trustees of the University, an introduction was secured to Professor Martin, whose sufficient distinction it was to have been an associate of Huxley, that grand Napoleon of biologic science, who had already enthralled the youth of two continents. I called on Professor Martin at his rooms and my spirits were lightened when I saw a very young man, he was then twenty-eight and looked younger, who treated me at once something like a companion. He was scarcely of medium height, of slight but well-developed frame. His head was rather small, the eyes blue and wide open, nose thin and fine, complexion fair and mustache blond. His dress was always strikingly neat without being foppish. I cannot but fancy that Martin then was homesick and keen to relish the devotion of one not far from his own age. Martin accepted me as his assistant in the biological laboratory at a stipend of $250 for the first six months. Not for many months did I suspect that this was at first a private and not a University appointment.

Martin's ability as a teacher is attested by the eminence of many pupils; his talent as an investigator is recorded in the literature of physiology; but the personality of the man, the kindly tact, the sincerity, the loyalty to truth and the indefinable emanation that reaches from man to man, the memory of these is apt to fail with the heartbeats of his companions. I well remember the first week of preparation for class work. There was as yet no laboratory "Diener" and a hundred tasks of household preparation were to be completed in advance. Martin was kinder than he could have known when he stood beside his assistant washing bottles for reagents; and in this, as in every other field, what would have sorely hurt as a menial service he turned into the routine of technical manipulation.

While he never gave way to sentimentality, his invariable kindliness where he had bestowed confidence withstood every strain of daily intercourse. On one occasion he loaned me overnight the manuscript of an important public address which was to be published. Next morning the roll was missing and apparently lost beyond repair, but the delinquent was the only one ruffled by the accident. To his great joy the papers were found to have been left on the counter of a friendly shopkeeper. For one of his public lectures before a fashionable, and chiefly feminine, audience plans had been devised for the demonstration on the projection screen of familiar physiological activities such as muscular contraction, reflex action and the heart beat in the frog. My business was to prepare the tissues and make them work. Unfortunately the apparatus was not available for proper rehearsal and when the fateful hour came, the nerves and muscles rebelled at the "lime light." Martin would graphically describe a function and then call for demonstration. Again and again I failed him and things looked desperate, when he asked in the gloom of turned down light and with accents between a sob and a groan, "Sewall, is your heart going?" Humiliation was relieved by the titter that restored the humor of that fair audience.

A lecturer might well feel murderous towards an assistant who so failed him, but if Martin felt that way he gave no sign.

Leading women of that day seemed more interested in general culture than in politics. For a considerable period Martin made weekly visits to New York to talk biology before a woman's club of exclusive personnel. In this and similar ways not only was scientific instruction of the right sort widely diffused but individual sympathy with scientific aims and methods was infused into social and civic leaders of various communities. It may easily be surmised that the present annoying agitation against animal experimentation might lose at least the co-operation of the sane and truthful element of society were scientific teachers generally in the habit of imparting by *viva voce* methods and colloquial intercourse their technical thoughts and aims.

One marvels at the wisdom of those early directors of the University policy. No effort was spared, apparently, to direct, uplift and fulfill the higher ambitions of the people of Baltimore. This people of peculiar sensitiveness, with unmeasured potential power, could have easily been irritated into an antagonistic force against the infant university. But even before the doors were opened and beginning with the public inaugural address by Professor Huxley, the people of Baltimore were taught that this institution was primarily for them and their children. They were made to feel at home in its lecture halls, its class rooms and its laboratories. In this social knitting of fellowship between the University and the community Professor Martin took a leading part. Endowed with social instinct and a cultivated *savoir faire* he was welcomed into the exclusive social circles of the community and early numbered warm friends in the admirable upper stratum of the medical profession of the city. Not until many years after was the medical school of the University opened, and I cannot think but that the preliminary moulding of local medical sentiment by Martin was a powerful stimulus to that valuable and hearty co-operation given by the best element of the profession to the medical school in its early days. The University of Maryland was at that time in fact and tradition the only medical school in Baltimore. Curiously enough, since the establishment of the Johns Hopkins medical department with its unequalled standards, the medical schools of the city have multiplied to the number of eight, few of which have attained qualifications endorsed by the investigating committee of the Carnegie Foundation. Though Martin's special training had been in animal physiology the title of his position was that of Professor of Biology and the first course offered in the laboratory was one

in general biology, following the lines of the textbook by Huxley and Martin. The personnel of the first class was drawn chiefly from the more ambitious students of the University of Maryland and younger graduates of that school. The precious influence of those early days of halting development is attested in the careers of many who there first tested the exultant freedom of scientific thought. Councilman was one of those pupils and often has he eagerly acknowledged his debt to Martin for kindling and shaping his early ambitions. There Booker laboriously laid the foundation for the admirable work he later did. Rivers, now of Denver, was in that earliest class. Later, Sternberg, just winning his spurs in bacteriology, was cordially given the run of the laboratory and there developed some of the essential researches on which his scientific reputation rests. And, incidentally, it may be remarked that, in my belief, the vast uplift which the medical and hygienic standards of the government medical service has witnessed in the past quarter century has been chiefly due to the influence of the biological departments of the Johns Hopkins University, first through the stimulus given by Martin and later by the precious association enjoyed by workers with Welch. There was illustrated the very ideal of pedagogy in which the soul of the teacher combined with the soul of the pupil and charged it with a force which irresistibly impelled to the search for revelation in Nature. It may well be doubted whether without this teaching there would have been as we know them in person or in memory, a Reed, a Carroll, a Gorgas or a Lazear. Without this teaching it is probable that yellow fever would have remained a mysterious miasm and the attempt to trench the continent at Panama would have been a disastrous failure.

In the second or third year of the laboratory young men fresh from college, and with vastly better preliminary training than those from the medical school, began to seek postgraduate instruction. Among these one quiet boy, by virtue of his clear judgment and competent grasp of the problems presented, soon became singled out from the rest of the class as that boon to the teacher, a sort of intellectual reagent by which the efficiency of the instruction might be tested. None of us dreamed that this lad, W. H. Howell, was in training to take up the task which Martin was to relinquish and to keep the physiological laboratory of Johns Hopkins in the forefront of the friendly rivals for whose existence it was largely responsible.

Looking back over the history of those days one must marvel at the felicity with which Martin made and then developed opportunities in the unbroken field before him. Courses in practical biology and practical physiology formed the routine of laboratory work. But soon there were established accessory classes in demonstration and practice. A selected number of the teachers of Baltimore were offered a course of study on Saturday mornings. Listening first to a brief descriptive lecture by the professor, they then adjourned to the laboratory and with their own hands and eyes carried on for two or three hours such a nature study as had not been conceived in those days. It was a duty of the writer to prepare material for that Saturday's class and the obligation fully occupied the spare time of the preceding week. The physicians of the community were invited to a course of physiological demonstrations and many eagerly availed themselves of the opportunity. Martin's unselfish and impelling nature sought the utmost development of all about him. The present writer had no sooner attained a defensible grasp of histological material and technique than he was induced to offer a private course in histology to medical students and was allowed to retain the fees therefor.

Martin soon came to be looked upon as the scientific exponent of the medical profession and through lectures and practical demonstrations he illuminated the minds and raised the ideals of the more ambitious members of the cult. With infinite tact he made abstruse subjects so plain and practical that his hearers often volunteered as real students and helpers. He beguiled a medical audience into a feeling of familiarity with profound subjects and at the end the listeners had actually acquired something.

W. K. Brooks was originally appointed Fellow in the Department of Biology, but at the outset it became apparent that his acquirements and capacity were preeminent and he gradually took over the distinctly zoölogical side of the instruction. Brooks was one of the very few men I have known who seemed to me to be born philosophers. What I understand to be the philosophic method was to him not like a suit of clothes to be left in the class room but was his very skin and indispensable. His viewpoint of all phenomena was such as one might imagine actuated the Genius of Nature itself. A fireside talk with him was almost an intellectual carousal but, withal, leaving one fresher and better satisfied.

After we had been going some four years, the writer having moved on to a Fellowship and then to the post of Associate in Biology, W. T. Sedgwick, newly from Yale, was put in charge of practical instruction. We made a most harmonious team. He confided to me at the outset that he didn't know anything about the subject. I confessed to being in much the same fix but that we wouldn't say anything about it. Sedgwick was gifted with that precious influence, which is the most valuable faculty of the physician in the sick room, the power of diffusing confidence. His calm, critical yet kindly partnership was distinctly to the good of the department. I can hardly doubt that in return, the training he received in Baltimore was the corner stone to that brilliant career upon which he was soon to enter at the Massachusetts Institute of Technology.

Most teachers, perhaps, on leaving the class room or laboratory are glad to shun the faces that duty makes familiar throughout the day, but Professor Martin after his marriage invited pupils to a weekly informal conference at his home where with his talented wife he supplemented the impersonal relations of the laboratory with the ties of social intercourse. The high grade associations which Martin had enjoyed, especially at Cambridge, no less put their stamp on his character than did the unique training in nature study under Huxley and Foster direct the current of his abilities. The absolute

unselfish singleness of purpose of the man to seek the truth in Nature and to be honest with his friends shone clear in every act, though he refrained from ostensibly preaching ethics. We hedge round with a wall of respect the slender group of those who have no private working legend, "What is there in it for me?"

No adequate estimate of the specific educational forces at work in the late seventies can fail to take into account the influence on the youth of that period of the intellectual atmosphere emanating from the doctrine of evolution. The "Descent of Man" appeared in 1871 and soon a strife was on between a protesting and enraged orthodoxy on the one hand and the, often iconoclastic, forces of thought-liberty on the other. Professor Huxley, known affectionately by those near him as the "General," as the commander of a ship is dubbed "the old man," was the splendid and aggressive leader of the Anglo-Saxon believers in evolution. It is not surprising that the internal tempest bred by thoughts of the supernatural in the mind of every thinking youth should have often found its outlet along the channels of reason as suggested by evolution when intolerant of the traditions of mysticism. To be frank, the popular notion that the prevailing spirit of the Johns Hopkins staff in those days, at least as regards the biological department, was "agnostic" was sufficiently correct. A corollary to this attitude could not but occur to me when, with something like a shock, I once heard Martin say in effect, "I am thirty years old today and am ready to quit; have had enough." The corollary is that something more than nature study is necessary to satisfy some of the affinities of man.

To my mind the most useful teaching of Martin's career is found in an analysis of the elements of his success. It was clear in his case, as has often been established in others, that his success depended on careful preparation for every effort made. I was very much impressed when, after two years special study of gastric digestion and he had appointed me to make my maiden lecture on the subject, he asked me a full month before the time whether I had prepared my lecture yet. The thought sprang to mind "It may be that this ultra-preparedness has something to do with Martin's success."

Again, once when we were giving parallel courses to the same class, he in the morning and I in the afternoon, he one day evidently ran out of prepared material and to my horror, being one of the audience, he deliberately appropriated the most harmonious thunder I had laboriously stored for the afternoon. I hastened to privately reproach him on the subject but he only replied "It doesn't matter; it will do them more good to hear it a second time." This reminds one of the summing up which a great teacher, Michael Foster, I think, made of his pedagogic experience: "Every year I put less into my lectures and say it over oftener." I can recall but two personal criticisms Martin ever made to me, one was because of a tendency to neglect to expound familiar and obvious details in making a physiological demonstration and the other was for a proneness to procrastinate the preparation for a remote exposition. Martin found time in 1880 to write an excellent textbook of physiology, "The Human Body," which became very popular in colleges; and in a short time a separate, condensed edition, "The Briefer Course," was prepared for use in secondary schools.

Nothing that I have said predicates for the Johns Hopkins University or its biological department a position of peculiar preeminence among American institutions of learning. Yet it is now a matter of history that to the University was conceded a unique position as an educational leader almost from the opening of its doors. With phenomenal wisdom the administrators of the University chose for the heads of its departments men who were not merely good lecturers but were investigators and sources of inspiration in their respective fields. The three departments of natural science established were all under the direction of men still far short of middle age. In those days the young men gathered there were all votaries of what Huxley called "the divine dipsomania of original research." Of inexpressible value to us, often ill-informed but earnest students, were the precepts and examples of leaders trained in the ways of making knowledge. Martin's achievements inculcated the encouraging lesson that the prime requisite of a successful investigator is not "genius" or even great talent, but above all, a faithful, unerring, insatiable desire for Truth as a point of view; to which must be added a working energy of indomitable persistence and guided by a faith that nothing happens without a reason.

Martin was not a voluminous writer. In his seventeen years of service in Baltimore there were produced by him but fifteen papers covering the results of original researches. Some of the work that Martin accomplished was truly epoch-making by reason of the fact that it led to methods which have been most fruitful in physiological discovery. Yet Martin's name is seldom mentioned in the literature thereof. Verily, in science as in commercial life, the promoter is not without a function to him who would reap from his sowing. Martin knew nothing of mathematics, yet his clear mind grasped the essentially mathematical method of dealing with the complex problems of biology; for he realized the necessity of attacking vital phenomena not *in toto*, as the clinical observer is forced to do, but through a study of the separate variables which combine to produce them. He frequently said, "We know a good deal about the skeletal muscle because we can isolate it and of the frog's heart for the same reason," and his mind evidently kept in view the importance of studying the various vital functions in disassociated organs.

I very well remember one morning, I think it was in the Fall of 1880, Martin said to me, in effect, "I could not sleep last night and the thought came to me that the problem of isolating the mammalian heart might be solved by getting a return circulation through the coronary vessels." The idea seemed reasonable and at the close of the day's work we anæsthetized a dog, prepared him for artificial respiration and then Professor Martin opened the chest and ligatured one by one the venæ cavæ and the aorta in such a way as to leave sufficient amount of blood in the heart itself. The heart con-

tinued to beat in a normal manner, the circuit made by the blood being from the right side, through the lungs to the left side and back through the coronary vessels in the heart wall to the right auricle again. Thus heart and lungs were completely isolated from the rest of the body and could be studied unaffected by the interference of factors foreign to itself. Martin grasped the full significance of his discovery and elaborated with infinite patience the practical details involved in submitting the isolated organ to experimental conditions. It was thought necessary to furnish the heart with an artificial supply of blood and accordingly defibrinated calf's blood was used and fed to the heart from a Mariotte's flask. The body of the dog and all the materials used in the experiment were inclosed within a glass walled hood of ample dimensions movable by ropes and pulleys over a shallow pan of zinc in which water was kept heated at a body temperature. In such an apparatus the isolated heart could be kept beating in a fairly normal fashion for upwards of five hours. The prosecution of such an experiment was exhausting to body and mind, yet for several years Martin lost no opportunity to press his work to a finish. Nothing could be a surer index of the clarity of mind in this investigator than the simple and fundamental data he sought to establish by his new method. We find his first paper entitled, "The Influence on the Pulse Rate of Variations of Arterial Pressure, of Venous Pressure and of Temperature." Again we have "The Direct Influence of Gradual Variations of Temperature upon the Rate of Beat of the Dog's Heart." Also, "The Aetion of Ethyl Alcohol upon the Dog's Heart," and so on through a series of some nine researches.* The paper upon the effect of temperature upon the heart beat was the subject of the Croonian lecture for 1883, and about this time the author was elected Fellow of the Royal Society.

The great strides which have been made towards a complete knowledge of cardiac physiology and, as an outcome, of clinical cardiac pathology in the past ten or fifteen years, have been made along the path first cleared by Martin. It was not until 1895, fourteen years after Martin's discovery, that Langendorff introduced his admirable and simple method of sustaining the isolated heart by a nutrient stream directed into the coronary vessels alone through a canula tied in the stump of the aorta. It seems little to the credit of physiologists that so long a time should have elapsed before so obvious a modification of Martin's procedure should have suggested itself. Isolation of the mammalian heart by the "Method of Langendorff" is now a common laboratory procedure. Probably few are aware of the real discoverer of the idea.

It is interesting to note the character of the problems with which Martin busied himself, and his persistent search for an *experimentum crucis*. Assisted by Sedgwick he apparently settled experimentally the disputed function of the internal intercostal muscles. They also succeeded in putting a canula in a coronary artery of the living dog's heart and directly measuring the blood pressure and pulse wave in the coronary system, though the great Cohnheim had laid down the dictum that occlusion of a main coronary artery was immediately fatal to the physiological action of the heart.

When one considers the prevision manifested in these researches of a quarter century back one cannot but deplore the loss to science of Martin's mind and wonder whether, with the richer material facts and profounder views of their meaning now current, he might not, if living today, be the acknowledged master in his chosen field. Perhaps, after all, it is only another of Nature's compensations that the story of life should be prone to end in anticlimax. It makes it easier to close the book. Failing in health and energy of application for some years, Martin resigned his professorship in 1893, at an age when he should have been in his prime—45 years. In a letter to me written from a sick room at that time his thought was all for the destiny of that Pure Physiology which he had labored so faithfully to nurture on American soil.

* *Vid.* Memorial Volume, "Physiological Papers," by H. Newell Martin. The Johns Hopkins Press, 1895.

MEDICAL NOTES ON THE DIVINE COMEDY OF DANTE ALIGHIERI.*

By P. H. Dernehl, M. D., Milwaukee, Wisconsin.

As a physician one cannot, in reading the Divine Comedy, escape being attracted by the frequent medical allusions it contains. It may appear of subordinate interest to attempt to draw from and present by itself its medical lore, and perhaps also imprudent in a physician to express an opinion on Dantean questions which in truth fall not within his sphere. The latter is in no wise my purpose. I have endeavored merely to present in collected form, making no pretense at completeness, such references as I believed might prove of interest in portraying something of the state of medical science in Dante's age and as might serve to shed some light upon his knowledge of medicine. I trust this may have been to no idle purpose.

To secure a finished picture of medicine, especially of ancient and medieval medicine, we are pressed to call upon the historian, philosopher and poet to supply that which the purely medical writers have withheld from us. Thus Homer reveals a wealth of medical information in the Iliad and Odyssey. Plato, the philosopher, wrote also of medical problems. To the historian, Thucydides, we owe the best account we possess of the plague of Athens. The medicine in Shakespeare has been made a subject by many writers. Molière has preserved for us

* All the quotations are taken from Longfellow's translation of the Divine Comedy. I have given it preference over the many others, first, because of the English translations, I believe it to be the one with which the American reader is most familiar, and, second, because, accepting the opinion of those best qualified to judge, his version is recognized as among the best in any tongue, and the most faithful and scholarly which the English language possesses.

phases of the medical life of the seventeenth century. How frequently we find in accounts of the plague of England (1663-65) quotations, describing its ravages, taken from Pepys' Diary. Choosing at random from among more recent writers, let us select George Eliot, who in Middlemarch, seeks to incorporate in Doctor Lydgate the struggles and aspirations of the profession in the nineteenth century, and Oliver Wendell Holmes, in whose purely literary writings, we are given so much of interest and worth drawn from a physician's daily life in his community. But where today can we find the old family doctor he depicts? We would seek in vain through the medical journals for an account of him. In like manner the Divine Comedy—the Mirror of the Middle Ages, as it has been termed—reveals much of medical interest, which deserves recognition, the more so because the medical literature of the Dantean period leaves much to be desired.

The Divine Comedy is an expression of all that the great genius of Dante was master. It is more than a medieval comprehension of dreams of the hereafter, abounding with legends and visions of the world to come. It is the one epic which embodies as no other has done the past and present, time and eternity. One cannot read it carefully without observing how closely, almost exclusively, Dante fixes his observation on human nature. Humanity itself with its faith and erudition, with its presentiments, with its joys and sorrows, peace and repose, with its strifes and toils, and with its virtues and vices is the fertile source of his theme. For that vast gathering of spirits which is introduced to discourse on such varied topics we glean that which the Divine Comedy contains of medical interest. What it portrays of medicine is as Dante and his time knew it.

Whether, if at all, Dante was schooled in the science of medicine remains conjecture. The opinions of his numerous commentators are at variance regarding this, and Dante in his writings has left no positive evidence. The consensus of opinion among his commentators appears to be that in large part his learning was acquired autodidactically and that later in life his eagerness for the acquisition of knowledge led him to pursue university study. His early training was gained in the schools of Florence. In these were taught the trivium and quadrivium, the first including grammar, logic and rhetoric; the second, music, arithmetic, geometry and astronomy. Among the universities, Padua, Bologna, Paris and even Oxford are accredited with having had him enrolled. Be that as it may, we are in total darkness whether or not while in attendance at any one of these institutions, Dante devoted any of his time to the study of medicine. We know that in 1297 he enrolled himself in the guild of physicians and apothecaries, being there qualified with the title "*Poeta.*" His enrolling as a member of a guild was probably done as a necessary preliminary requisite to his entering upon active politics. But why choose the mentioned guild in preference to others? Because among his ancestors were druggists; because Dante intended eventually to pursue medicine as a calling; because apothecaries, in his time, dealt also in books, and Dante was a lover of these; because to this guild belonged also artists, and Dante was a lover of art. These and other reasons are presented on the list of choice.

The "Guild of Doctors and Apothecaries of Florence" was incorporated in the twelfth century. It grew rapidly in importance during the thirteenth and fourteenth centuries, and soon became a very important power in the republic of Florence.

A statute applying to the physicians lays down that, "No doctor may be allowed to practice unless he has first been publicly examined by the consuls of the guild." To apply as an apothecary imposed no examination, as it did for a doctor, and required merely registration. Those engaged in the making and selling of books and other literary matter were members of this guild; so too the painters and engravers. The fact then that Dante enrolled as a member of this guild cannot well be taken as evidence that he devoted himself to the study of medicine in order to qualify as a member. We are told by no less an authority and student of Dante than Kraus, that Dante knew medicine and practiced it as a means of support while in exile. Lowell tells us that "to the trivium and quadrivium Dante afterward added painting, theology and medicine." Whether or not Dante was versed or trained in medicine the fact remains that he did not write as a physician. In attempting to interpret his medical references in the Divine Comedy it is often difficult to discriminate between what shall or shall not be regarded as such. A liberal interpretation must include many things, that are but the expression of a common knowledge held by all men of his time. For a better understanding of what the Divine Comedy contains of medical interest it may not be amiss to recall briefly the state of affairs under which medicine labored in the thirteenth and fourteenth centuries.

All medicine during this period was held fast by the ban of the inexorable idolatry of Galen, and, as did all learning in this period, suffered heavily under clerical, feudal and scholastic conceits. Under the oppression of a ruling despotism and mystical tendencies, a spirit of individual research could not flourish, and the men of medicine were known less by the merit of their works than by their love for instructing and the zeal they displayed in the propagation of such knowledge as they had borrowed from the ancients. However, the Arabic versions of Greek medicine had been rendered into Latin from the books of Rhazes, Albucasis, Avicenna and others, and this gave a worthy impulse to medical progress. The schools of Salerno, Bologna, Padua, Montpellier and Paris, as liberal institutions of learning, had reached and were advancing to a reputable height. But philosophy which was most ardently pursued at these institutions held medicine wrapt in its cloak, permitting it to become little more than a philosophical science. It tended on the one hand toward Galenism, on the other it conformed with the Arabic system or again strove along some new and untrodden medico-philosophical path. Under the heads of these various systems all observations were recorded blindly. That conditions such as these could produce but few real medical writers worthy to arrest our attention is clearly evident. Besides the universities, the cloisters were also seats

of medical learning. The Benedictines in particular occupied themselves much with medicine and even gave themselves to the practice of surgery, though frequently against the wishes of their superiors. Those who taught medicine at the universities and other institutions of learning usually also practiced it; they did little, however, with surgery, and spent much of their time commentating the works of the ancients. Of the practicing physicians proper, some had an established residence, others traveled from place to place. The former were usually men systematically trained at the universities and were granted the right to practice their art under certain provisions. These being laid down in an edict of Frederick II in 1224, by virtue of which no individual in the kingdom who had not been examined previously and created a master by the school of Salerno could practice. It required that the study of logic, that is philosophy and philology, be pursued for three years and a course in medicine, including surgery, for five years. The student had to furnish a certificate of legitimate birth and have attained his twenty-fifth year. He was examined publicly on the therapeutics of Galen, the first book of Avicenna and the aphorisms of Hippocrates. He could not enter legally into practice, however, until he had served a year as apprentice to an older and experienced physician. Besides these resident medicists, there were those who practiced as traveling scholars, going from place to place, often in company with a buffoon or jackrake, visiting the markets and places of public gathering, advertising their "wares." This species of charlatan played no small part in the practice of medicine during the whole of the Middle Ages. The pure surgeons of the day were obliged to follow the teachings of a faculty for one year. This period was devoted principally to the study of anatomy. Further knowledge pertaining to their art they gleaned from a master to whom they were apprenticed. They were given the title of *Magistri chirurgiae* and permitted to practice surgery only. Many of these were resident surgeons and members of guilds. Others, as surgeons of the short robe, traveled about performing, often brutally enough, operations for hernias, cutting for stone, doing operations upon the eye, among which couching took first rank, and always making sure to be out of reach of the avenger before the result became manifest. Lastly, there were the barbers and bathers, the former being privileged to do cupping and bleeding, extract teeth and set fractures and dislocations and execute various minor operations and often enough they were guilty of transgressing upon the field of the surgeons. The bathers, like the barbers, did cupping and bleeding and gave clysters.

During this period, too, medical superstition, growing as it did upon a soil so well prepared by vainglorious philosophy and by a scholasticism which had usurped all clear human reasoning, had reached a high stage. Faith in the healing influence of certain astrological phenomena was universal, as also the belief, heightened by religious fanaticism, that the divine influence could and always did alter and direct the functions of the body. Belief in the evil workings of the devil, the healing of the sick by the power of the saints and through relics, amulets and gems was in high favor throughout the Middle Ages and continued in vogue as late as the sixteenth and early seventeenth century. Closely associated with these beliefs was that in the magic art and magic medicine. Though condemned by early Christian emperors, its ideas still survived and its methods frequently shade so insensibly into the superstitution, yes, into the religion and philosophy of this period that it often becomes imposible to decide to which of these domains the one or the other belongs.

In the lowest Hell, where punishment for graver sins awaits the doomed, Dante sees among others the workers in the magic art. One of these Virgil points out to him as Michael Scott--

*** * * who of a verity**
Of magical illusions knew the game. (Inf. XX, 116.)

Scott, astrologer of the Hohenstauffen monarch, Frederick II, deserves our recognition as the supposed translator of Avicenna's commentary on Aristotle's De Animalibus. The workers in magic medicine who are associated with Scott in this Bolgia are referred to as they who

*** * * wrought their magic spells with herb and image.**
(Inf. XX, 123.)

The belief in the healing power of gems appears to have been strongly influenced by the writings of Michael Psellus (1020-1105), whose book on the therapeutic action of stones is frequently referred to in medieval medical literature. How deeply this belief had taken root we can gather from later medical writers. Cardan and Paracelsus gave space to its promulgation. From Sir Thomas Browne's Vulgar Errors, the sixth edition published in 1672, I quote the following. Browne writes: "That *lapis lazuli* hath in it a purgative faculty we know; that bezoar is antidotal, *lapis judaicus* diuretical, coral anti-epileptical we will not deny. That cornelians, jaspis, heliotropes and bloodstones may be of virtue to those intentions they are employed, experience and visible effects will make us grant. But that an amethyst prevents inebriation; that an emerald will break if worn in copulation; that a diamond laid under a pillow, will betray the incontinency of a wife; that a sapphire is preservative against enchantments; that the fume of an agate will avert a tempest or the wearing of a chrysophrase make one out of love with gold as some have delivered, we are yet, I confess to believe and in that infidelity are likely to end our days."

Dante refers several times to the mystic virtue of gems, recounting the ruby, topaz, heliotrope and sapphire. Led by Beatrice into the Empyrean, its splendor and brightness bereaves Dante of his vision, but with the aid of Beatrice and by the virtue derived of drinking from the waters of the river of light he becomes enabled to see,

Both of the Courts of Heaven made manifest. (Par. XXX, 96.)

Out of this river issued living sparks,
And on all sides sank down into the flowers,
Like unto rubies that are set in gold. (Par. XXX, 64.)

The water of this river, Beatrice informs him, he needs must drink that his sight might comprehend all the gladness of that Heaven. It is safe to assume that Dante's reference to the

ruby here rests upon the belief that the ruby powdered and taken in water cured diseases of the eyes.

It was during Dante's time that the veneration paid to the Virgin Mary, in earlier times very great, rose to an almost exclusive idolatry. By prayer her aid was invoked in the cure of all ailments, though her particular virtues in this respect were believed to manifest themselves at the natal hour. It is of interest in this connection to quote from the Calendaria of Cardanus (1505-1576) who by the aid of astrology affirms that in this event the request to the Virgin would be sure to be complied with, if on the first day of April at 8 a. m. a prayer invoking her aid were offered. On the fifth terrace of Purgatory, Dante hears uttered amid the weeping,

* * * * * "Sweet Mary!"
* * * * * * * *
Even as a woman doth who is in child-birth. (Purg. XX, 19.)

In Paradise the spirit of his ancestor Cacciaguida recites of the beauty and simplicity of Florentine customs in his day and adds to such a beautiful life,

Did Mary give me, with loud cries invoked. (Par. XV, 133.)

The same spirit relating of his birth, says of this,

From uttering of the *Ave*, till the birth
In which my mother, who is now a saint,
Of me was lightened who had been her burden. (Par. XVI, 34.)

As mentioned, faith in the medical virtues of the saints and the evil doings of the devil was markedly manifest during the Middle Ages and was shared by all classes. As late as the seventeenth century we find traces of this belief still prevalent among many members of the medical profession.

In the pageant of the Church Militant St. Luke is introduced as

One showed himself as one of the disciples
Of that supreme Hippocrates, whom nature
Made for the animals she holds most dear. (Purg. XXIX, 136.)

St. Luke, writer of the Acts of the Apostles, is supposed to have been both an artist and a physician. Whether he was ordained as healer of any one specific sickness or exercised this function at large I have been unable to learn with certainty. In the Inferno the aid rendered Constantine by St. Sylvester in curing him of his leprosy finds expression in

But even as Constantine sought out Sylvester
To cure his leprosy * * * * (Inf. XXVII, 94.)

This probably finds its source in the *Legenda Aurea,* by de Voragine (1230-1298). I have been unable to find anywhere that Sylvester's aid was specially invoked in the cure of leprosy. Under this heading may be added one further reference. In Paradise, Dante is examined by St. John on Christian love. By the refulgent flame of that saint he becomes so dazzled as to be for the moment bereft of his sight. Beatrice, who

* * * has in her look
The power the hand of Ananias had. (Par. XXVI, 12.)

gives Dante back clear vision. It may appear that these references are destitute of medical worth, but in the light of the Middle Ages, the era of miracles, a belief in them was firmly fixed and largely through the contributions and teachings of the clergy. Be it remembered that Paré (1517-1590) was never able to quite divest himself of his belief in saints and monsters. Firmer and more enduring was the belief in the agency of the devil, afflicting humanity with disease in its various forms. The epidemic of St. Vitus's dance in the fourteenth century, for instance, was attributed to the evil workings of the devil. Not alone in the creation of disease were his activities made manifest, but as Martin Luther, in accordance with the existing belief, seeks to have us believe, the infernal spirit was not loath to assume the rights which should be permitted only to the husband: "Es ist wahrlich ein greulich schrecklich Exempel dass der Teufel kann die Leute plagen dass er auch Kinder zeuget" ("Tischreden"). Among the references expressing the evil workings of the devil, the following one serves well to portray this medieval conception:

And as he who falls, and knows not how,
By force of demons who to earth, down drag him,
Or other oppilation that binds man,
When he arises and around him looks,
Wholly bewildered by the mighty anguish
Which he has suffered, and in looking sighs. (Inf. XXIV, 112.)

By "*other oppilation,*" I infer with Dr. Carlyle and Benvenuto that Dante would have us understand the fits of epilepsy. This surely is a more likely interpretation than that given by Jeremy Taylor, who believed that by it is meant gout, dropsy or catarrh. The epileptics, and insane in particular, were believed to be the abode of the devil, a belief first propounded by Origenes, and later greatly furthered by the church. The treatment, often most inhuman, consisted also in prayers, pilgrimages and exorcisms or in the administration of remedies assumed to contain divine puissance. Thus Peter of Spain († 1277):

Who down below in volumnes twelve is shining. (Par. XII, 134.)

tells in his *Thesaurus pauperum,* that the charms of the monks are discarded by him, but that to keep free from epilepsy one needs but suspend about the neck a piece of paper upon which are written the names of the Saints Caspar, Melchior and Balthasar.

Reaching the tenth gulf of hell, Dante meets the forgers and alchemists, who as punishment for their offenses are afflicted with diverse plagues and diseases. This gives him occasion to liken the intensity of their affliction to the sufferings during the plague of Aegina.

I do not think a sadder sight to see
Was in Ægina the whole people sick,
(When was the air so full of pestilence,
The animals, down to the little worm,
All fell, * * * * * *
* * * * * * * *)
Than was it to behold through that dark valley
The spirits languishing in divers heaps.
This on the belly, that upon the back
One of the other lay, and others crawling
Shifted themselves along the dismal road.
We step by step went onward without speech,
Gazing upon and listening to the sick
Who had not strength enough to lift their bodies.
(Inf. XXIX, 58.)

The source of the picture which Dante here gives is very probably borrowed from Ovid's account of the plague of Ægina (Metamorphoses, VII), an excerpt of which from Stonestreet's translation will prove of interest.

Their black dry tongues are swelled and scarce can move,
And short thick sighs from panting lungs are drove.
They gape for air, with flatt'ring hopes t'abate
Their raging flames, but that augments their heat.
No bed, no covering can the wretches bear,
But, on the ground, exposed to open air,
They lie, and hope to find a pleasing coolness there.
The suff'ring earth, with that oppression curst,
Returns the heat which they imparted first.
* * * * * * *
Here one, with fainting steps, does slowly creep
O'er heaps of dead, and straight augments the heap;
Another, while his strength and tongue prevailed,
Bewails his friend, and falls himself bewailed;
This with imploring look surveys the skies,
The last dear office of his closing eyes,
But finds the Heavens implacable and dies.

In the sixteenth Canto of Paradise, Dante deplores the downfall and degeneracy of Florence and its citizens, a cause for which he sees in the introduction of families from the neighboring countries and villages. He is told by Cacciaguida that,

Ever the intermingling of the people
Has been the source of malady in cities,
As in the body food it surfeits on. (Par. XVI, 67.)

and

To hear how races waste themselves away,
Will seem to thee no novel thing nor hard,
Seeing that even cities have an end. (Par. XVI. 76.)

These lines have been variously interpreted. Longfellow writes: "Boccaccio seems to have caught something of the spirit of this canto, when lamenting the desolation of Florence by the plague in 1348." It appears that following the epidemics of Rome (1167) and that of Venice (1172) there continued to occur in Europe at intervals, with more or less abatement, outbreaks of a prevailing *pest,* to culminate again in that horrible, devastating epidemic, the Black Death, which it is estimated depopulated Europe during the three years, 1348-1351, of twenty-five million human lives. It is unfortunate so careful a recorder and acute observer as Dante has left us no account of any plague visitation, for it appears conceivable that if not an eye witness he must have had plague horrors related to him. The view of Dante that the intermingling of people is an exciting cause of the spread of diseases in cities was expressed by both Plutarch and Thucydides centuries before. Thucydides (Jowett's translation) writes of the plague of Athens: "As to its probable origin or the causes which might or could have produced such a disturbance of nature, every man, whether a physician or not, will give his own opinion. . . . . The crowding of the people out of the country into the city aggravated the misery; and the newly arrived suffered most. For, having no houses of their own, but inhabiting in the height of summer stifling huts, the mortality among them was dreadful and they perished in wild disorder." Plutarch (Langhorn's translation) writes of this plague, that the people were persuaded, "that the sickness was occasioned by the multitude of out dwellers flocking into the city and a number of people stuffed together in the height of summer in small huts and close cabins where they were forced to live a lazy inactive life, instead of breathing the pure open air to which they had been accustomed."

With the anatomical references in the Divine Comedy must be associated those to physiology, for it was not until the late sixteenth and the seventeenth centuries that physiology was placed upon a pure rational and scientific basis through the labors of such masters as Galileo, Newton and Borelli in physics and in particular through the efforts and discoveries of Harvey, Hales, Magendie, Spallanzani and others of their type, but especially those of Haller, who has been and is still honored with the proud appelation of the father of physiology. The anatomy and physiology in Dante is largely that propounded by Galen. As deserving of notice Galen was the first to apply methods of experimentation and vivisection to physiology (Baas). Unfortunately he so overburdened his teachings of this science with false speculations and visionary conceits that these more than his experimental science left their impress upon the Middle Ages. To enter upon the physiology of Galen would lead beyond the confines of this paper. It, as did all of what was Galen's, exercised a paramount influence over medicine and was most firmly and slavishly adhered to.

For a better interpretation of the medical references that follow a brief outline of the salient points of Galen's physiology or better philosophico-physiological views may not be amiss. Galen believed that in man there are three actuating impulses—namely: spirits, humors and solids. The solids he divided into simple or similar and organic or compound. The former being represented by the bones, flesh, nerves, etc., the latter by the arms, legs, head, etc., because these are formed of the several similar parts. The dynamical forces of the soul or *pneuma* he divides, with Hippocrates and Aristotle, into four primordial qualities: heat, cold, dryness and humidity. These by their individual or united action influence all transformations of the human system. This pneuma vitalizes in the body a natural spirit, located in the liver and renal veins; an animal spirit in the brain and nerves, and a vital spirit in the arteries and heart. Subordinate to these are special faculties of the body that function occasionally, as the attractive, the repulsive, the retentive and the secreting faculties. The natural spirits originating with the veins in the liver proceed from thence with the blood to the heart, to be mixed with air, which that viscus attracts from the lungs, and uniting with it forms the vital spirit. This is then conducted by the arteries to all parts of the system, but chiefly to the brain where it is converted into the animal spirit. By these essences the action of production, nutrition and growth are maintained.

From the general character of Galen's presentation of the distribution of the sanguinary fluids it is a rational conclusion, perhaps, to assume his practical acquaintanceship with the circulation of the blood, but whether, as some medico-historical writers would have us believe, a knowledge of the utility of the

venous valves and of the true function of the heart was alone essential to deck him with the laurels that have come to Harvey had better be relegated to the realm of fruitless speculation.

Of more than common interest are the references found in the Divine Comedy relating to the circulatory system. Much stress has been laid upon the fact that Dante speaks of the pulse and distinguishes between veins and arteries, and upon this fact alone several of his commentators have chosen to base, in part at least, the contention that Dante knew medicine, or would infer that he antedated Harvey even. Thus Schlosser in his *Welt Geschichte* writes, "Anatomie und Physiologie [kannte er] besser als man für seine Zeiten denken sollte—Erst durch Harvey wurde nämlich die Lehre vom Blutlauf diesseits der Alpen verbreitet. Dante deutet aber gleich in Anfange seines Gedichts auf Puls und Blutadern hin." The passage to which Schlosser has reference occurs in the first canto of the Inferno. Dante, being driven back from the path he pursued by the she wolf, implores Virgil's protection with

"Do thou protect me from her, famous Sage,
For she doth make my veins and pulses tremble." (Inf. I, 89.)

In recounting the humiliation of Provenzan Salvani, to which he bowed himself, that he might save his friend, the shame of which was so great that

He brought himself to tremble in each vein. (Purg. XI, 138.)

This throbbing of the pulses finds more forcible expression when Dante finds himself deprived of Virgil's guidance in

* * * * * "Not a drachm
Of blood remains in me that doth not tremble." (Purg. XXX, 46.)

Whether or not Dante distinguished arterial from venous blood is perhaps given expression to in the ninth canto of Purgatory, where Dante likens the third and uppermost stairs of the gate leading to that Heaven, and which is made of porphyry, to the color of blood—

* * * as flaming red
As blood that from a vein is spirting forth. (Purg. IX, 101.)

Lanfranchi († 1315) is said to have been the first to distinguish between arterial and venous hemorrhage. Dante appears to have shared with Galen the belief prevalent also in his own time, that the blood was the seat of life. This is expressed in several passages. The shade of De Vinea tells Dante that the fidelity which he, Frederick's chancellor, bore his master was of such magnitude that he thereby lost his sleep and *pulses* (life) (Inf. XIII, 63). In Purgatory Jacopo del Cassero, reciting his past, speaks of his death from

* * * * the deep wounds, through which
Issued the blood wherein I had my seat. (Purg. V, 73.)

In the same book we are told that Christ liberated us with his *veins* (Purg. XXIII, 74).

It is rather striking to note the frequent references Dante makes to vision, its anatomy and physiology. The flashing, dazzling, brilliant lights in Purgatory and Paradise naturally call for expressions indicating the effect on the vision. However, the fact that he was interested in and busied himself with optics, and at one time suffered from severe ocular trouble, appears to have left a profound impress upon him. He speaks of it in the *Convito,* saying that the stars appeared to him as seen through a fog, and that he regained his clear vision only after a lengthy rest of his eyes in dark and cool surroundings and by the application of cold compresses, and this may naturally have rendered him more acutely sensitive to matters pertaining to vision. The effects of the bright lights are well expressed in

Even as a man who gazes, and endeavors
To see the eclipsing of the sun a little,
And, who by seeing sightless doth become,
So I became before that latest fire. (Par. XXV, 118.)

And that condition of the sight which is
In eyes but lately smitten by the sun
Bereft me of my vision some short while. (Purg. XXXII, 10.)

We meet with frequent references to squint and are told that as volition moves the eyes, they

Must needs together shut and lift themselves. (Par. XII, 26.)

We are told of spirits who carried their chin lifted upward like a blind man. To note the approach of an angel, who opens to Virgil and Dante the gates of the city of Dis, Virgil calls upon Dante to

* * * * "Direct the nerve
Of vision now along that ancient foam." (Inf. IX, 73.)

That the optic nerve effected the sight by having the rays of light intercepted and conducted to it by the *spirits* which are found between the lens and choroid was the accepted opinion in Dante's age. In making known to Dante that the departed spirits know things past and to come but are ignorant of things present, a spirit tells him:

"We see, like those who have imperfect sight,
The things," he said, "that distant are from us." (Inf. X, 100.)

We can safely infer, I think, that Dante has in mind the condition of "old sight" or presbyopia.

Roger Bacon (1214-1292 (1298)) knew lenses and that they were useful for near vision in the old. For optical purposes they appear to have been ground first about 1285 by a certain Salvino degli Armati, said to have died in 1317. A monk of Pisa, Alexander della Spina, who died in 1313, also has been accredited with the invention of spectacles and with the promotion of their use. So we see that lenses for optical purposes really came generally into use after Dante's time and that presbyopia the cause of the "imperfect sight," that sees only, "the things that distant are from us" then went uncorrected.

In the Inferno we find the largest number of references of a purely anatomical nature. These are for the most part, in fact almost entirely, very general. The spirits in the Inferno, suffering the tortures of the condemned, having their forms vivisected, torn and mutilated, their every parts exposed, and meeting our poet thus, would naturally call upon the anatomical knowledge of Dante to give an adequate account of what he saw. This is done free from all descriptive exactness, with an aim to present the tortures of Hell in the most awful and

terrible light, the better to work upon the feelings of men. The few quotations I give will illustrate the form deseriptive anatomy takes in the poem. In the ninth gulf of Hell, Dante meets with Mahomet who is,

Rent from the chin to where one breaketh wind.
Between his legs were hanging down his entrails;
His heart was visible, and the dismal sack
That maketh excrement of what is eaten. (Inf. XXVIII, 24.)

Another shade speaks these words:

Parted do I now bear my brain, alas!
From its beginning, which is in this trunk.[1] (Inf. XXVIII, 140.)

He sees a demon elutch a sinner by

* * * the sinews of the feet.[2] (Inf. XXI, 36.)

One unfortunate is transfixed by a serpent

There where the neck is knotted to the shoulders.[3]
(Inf. XXIV, 98.)

Still another is pierced through

* * * in that part[4] * * * whereat is first received
Our aliment * * * * * (Inf. XXV, 85.)

Cary translates this passage, "In that part whence our life is nourished first—" (*Donde prima é preso nostro alimento*). It was generally held down to Dante's time that the human fœtus breathed and was nourished through the umbilieus and by sucking upon the cotyledons. This opinion is probably based upon the study of the placentæ in the higher mammals, espeeially the pig, which were used almost exelusively for anatomical studies in the Middle Ages, and the results obtained were assumed to apply also to man. We ean readily understand the faith in the mentioned belief if we recall that in the non-deeiduate plaeentæ (the forms most eommonly met with in the animals thus employed) the chorionie villi are eoncentrated into definite patches or eotyledons, which at birth separate from the uterine mucous membrane, without tearing the latter away. The spirit of Guido Count of Montefeltro tells Dante that the deeds he did were given him by his mother

While I was still the form of bone and pulp. (Inf. XXVII, 73.)

This passage eonforms with the belief current during the greater part of the Middle Ages, that from the semen are first formed the membranes—"pulp"—a portion of these are then transformed into eartilage and bone, another into blood vessels, fibers, nerves and so on. In another passage Dante refers to his position standing next to Virgil as being

Upon that side where people have their hearts. (Purg. X, 48.)

In connection with this line one should recall that Galen, basing his opinion upon the finding in animals, assigned also to the human heart, a position in the eenter of the thoracie eavity. It remained so until Vesalius (1513-1564) gave it its true position.

Perhaps of greatest interest among the medical refereuces in the entire Divine Comedy is the following. Dante, seeking to inform himself on the natural process involved in the birth and development of the human body, begs Virgil to enlighten him. Virgil prays Statius that he give to our poet the enlightment sought. Statius then turns to Dante with

* * * * * "Son, if these words of mine
Thy mind doth contemplate and doth receive,
They'll be thy light unto the How thou sayest.
The perfect blood, which never is drunk up
Into the thirsty veins, and which remaineth
Like food that from the table thou removest,
Takes in the heart for all the human members
Virtue informative, as being that
Which to be changed to them goes through the veins.
Again digest, descends it where 't is better
Silent to be than say; and then drops thence,
Upon another's blood in natural vase.
There one together with the other mingles,
One to be passive meant, the other active
By reason of the perfect place it springs from;
And being conjoined, begins to operate,
Coagulating first, then vivifying
What for its matter it had made consistent.
The active virtue, being made a soul
As of a plant (in so far different,
This on the way is, that arrived already)
Then works so much, that now it moves and feels
Like a sea-fungus, and then undertakes
To organize the powers whose seed it is.
Now, Son, dilates and now distends itself
The virtue from the generator's heart,
Where nature is intent, on all the members.
But how from animal it man becomes
Thou dost not see as yet; this is a point
Which made a wiser man than thou once err
So far, that in his doctrine separate
He made the soul from possible intellect,
For he no organ saw by this assumed.
Open thy breast unto the truth that's coming,
And know that, just as soon as in the fœtus
The articulation of the brain is perfect,
The primal Motor turns to it well pleased
At so great art of nature, and inspires
A spirit new with virtue all replete,
Which what it finds there active doth attract
Into its substance, and becomes one soul,
Which lives, and feels, and on itself revolves.
And that thou less may wonder at my word,
Behold the sun's heat, which becometh wine,
Joined to the juice that from the vine distils.
Whenever Lachesis hath no more thread,
It separates from the flesh, and virtually
Bears with itself the human and divine;
The other faculties are voiceless all;
The memory, the intelligence, and the will
In action far more vigorous than before.
Without a pause it falleth of itself
In marvellous way on one shore or the other;
There of its roads it first is cognizant.
Soon as the place there circumscribeth it,
The virtue informative rays round about,
As, and as much as, in the living members.
And even as the air, when full of rain,
By alien rays that are therein reflected,
With divers colors shows itself adorned,
So there the neighboring air doth shape itself

[1] Spinal cord.
[2] Tendon of Achilles.
[3] Seventh cervical vertebra.
[4] The navel.

Into that form which doth impress upon it
Virtually the soul that has stood still.
And then in manner of the little flame,
Which followeth the fire where'er it shifts,
After the spirit followeth its new form.
Since afterwards it takes from this its semblance,
It is called shade; and thence it organizes
Thereafter every sense, even to the sight.
Thence is it that we speak, and thence we laugh;
Thence is it that we form the tears and sighs,

* * * * * * *

According as impress us, our desires
And other affections, so the shade is shaped,
And this is cause of what thou wonderest at." (Purg. XXV, 33.)

I have given this discourse of Statius thus complete, both for its medical interest and for its exemplifying, perhaps better than any other one passage in the Divine Comedy, the wonderful power of Dante in blending into poetry his science, philosophy and theology. Comments upon this passage are not wanting. Averroës, Thomas Aquinas, Galen, Aristotle and Hippocrates are mentioned as co-contributors. Quotations from the lengthy dissertations of these authors bearing on this interesting subject cannot be given here, but a few brief notes may serve to add interest to it. The *perfect blood* which is not taken up by the veins, is the arterial, the abode of the vital spirits, the venous blood serving merely in nutrition. In the heart the blood is perfected; this appears purely an adoption from Galen. Dante's view relative to the "mingling" of the sexual elements to which he refers as blood, is expressed figuratively. The male element, the semen, was believed even in very ancient times to contribute directly as such in the formation of the fœtus, for Hippocrates and Aristotle taught that it came from all parts of the body, and Galen from the blood in the testicle. The female element was generally also regarded as semen; this Galen leads from the ovary downward through the excretory ducts (the Fallopian tubes) and during and after coition, believes it to be uniformly mixed with the male element. Hippocrates and Aristotle held the female semen to be a vaginal secretion which during coition was increased in quantity. Aristotle states that the female projects her semen into the os uteri, where also that from the male is received; these mingling are from thence drawn into the uterus by inhalation, in the manner we inhale through mouth or nostril. Dioscorides, whom Dante mentions by name, and Athenæus, were of the opinion that in the female the menstrual blood serves as the material mass and that the male semen gives form to the new life. The conception that one of the elements is passive and the other active is probably also borrowed from Galen, who taught that the semen of the male was hotter and of denser consistency than that of the female, which latter in accordance with the greater "coldness of women," was colder and very fluid and acted merely as an excipient and nutritive material, giving rise to the fœtal membranes only, while the male semen was concerned in the making of the brain, the seat of the rational soul. The comparison Dante draws between the vegetative soul of man and that of the plant is this, that in man it must be developed, whereas in plants it is from the first complete. In man the vegetative soul in its development is converted into the sensitive soul. The "man" referred to by Statius as wiser than Dante is generally accepted to be Averroës. He who taught that the minds of all men were pervaded by one and the same universal intellect. It may be added that science and philosophy were confirmed in the opinion that the soul of the new life was breathed into it by God.

The purely medical references, *i. e.*, to internal medicine, leave no doubt that Dante was in possession of more than a lay knowledge of this branch of medical science. It is markedly apparent that, as compared to the purely anatomical references, these are characterized by a much greater descriptive exactness, denoting a keener study and insight; nor is this to be wondered at if we stop to recall the state into which anatomy had lapsed during the thirteenth and early fourteenth centuries. Medicine, through the impulse given it by the Arabs and by the freer dissemination of Greek medicine, continued more active and certainly, though in small measure, progressive, while anatomy on the contrary remained where Galen had left it.

Leprosy, so prevalent during the thirteenth century, is frequently referred to by Dante. He tells of two spirits so afflicted:

I saw two sitting leaned against each other,
As leans in heating platter against platter,
From head to foot bespotted o'er with scabs;
And never saw I plied a currycomb
By stable-boy for whom his master waits,
Or him who keeps awake unwillingly,
As every one was plying fast the bite
Of nails upon himself, for the great rage
Of itching which no other succor had.
And the nails downward with them dragged the scab,
In fashion as a knife the scales of bream,
Or any other fish that has them largest. (Inf. XXIX, 73.)

Evidently Dante seeks to picture what we today would term nodular or tubercular leprosy, in the advanced stage of which there is frequently associated pain, irritation and desquamation, which latter when excessive gives rise to an appearance not unlike that of ichthyosis, whereupon rests the poet's reference to the scales of fish. The ultimate loss of the nails in this disease finds expression in these words, addressed by Virgil to a leper who plies himself with scratching:

"* * * so may thy nails suffice thee
To all eternity unto this work." (Inf. XXIX, 89.)

Dante meeting his friend Forese among the spirits in Purgatory, recognizes him only by hearing his voice, and is appealed to with

"Ah, do not look at this dry leprosy,"
Entreated he, "which doth my skin discolor,
Nor at default of flesh that I may have." (Purg. XXIII, 49.)

The nodular form of leprosy, attacking frequently first the face and ears, often enlarging these and giving rise to a massing of nodules on the brow, with a consequent deepening of the natural furrows, especially at the root of the nose, produces a peculiar lion-like aspect, to which the ancients gave the name

of *leontiasis*. If we picture Forese so afflicted we can well see why Dante should have failed to recognize him.

The crusaders were largely instrumental in disseminating leprosy in Europe. It had reached its height at about the time that Dante lived, abating gradually until in the latter part of the sixteenth century it disappeared practically from the list of endemic diseases in middle Europe. The belief in its contagious nature, established in ancient times, led to the isolation of those suffering with it. In Europe and especially in Italy were special institutions (*lazzeretti*) erected for lepers, mostly in secluded places or beyond the city gates. The inmates of these were under general surveillance, and were given in many places special clothing, marked to indicate their affliction, or had to carry a wooden rattle to make known their approach or a cane with which to point out or touch what they wished. Means of support other than begging was denied them, and they were generally shunned or treated as outcasts. This is expressed in an address of Dante to two spirits—

"Let not your foul and loathsome punishment
Make you afraid to show yourselves to me." (Inf. XXIX, 107.)

A further great scourge, widespread over most of Italy and southern Europe, was malaria. A short excerpt taken from Murray's Handbook of Central Italy, depicting the devastation of malaria in Italy, is not without interest in this connection. In reading of the Lake of Bolsena, in the vicinity of Rome, we are informed that, "The treacherous beauty of the lake conceals malaria in its most fatal forms; and its shores, although there are no traces of a marsh, are deserted, excepting where a few sickly hamlets are scattered on their western slopes. The ground is cultivated in many places down to the water's edge, but the laborers dare not sleep for a single night, during the summer or autumn, on the plains where they work by day; and a large tract of beautiful and productive country is reduced to a perfect solitude by this invisible calamity. Nothing can be more striking than the appearance of the lake, without a single sail upon its waters, and with scarcely a human habitation within sight of Bolsena; and nothing perhaps can give the traveler who visits Italy for the first time a more impressive idea of the effects of malaria." In the tenth gulf of Hell the spirits' suffering is intense, such that Dante writes of it,

What pain would be if from the hospitals
Of Valdichiana, 'twixt July and September,
And of Maremma and Sardinia
All the diseases in one moat were gathered,
Such was it here, and such stench came from it
As from putrescent limbs is wont to issue. (Inf. XXIX, 46.)

Dante's mention of the time "'twixt July and September" indicates that period of the year in which malaria was at its worst. The marshy regions of Italy, the Maremma, along the coast of the Tyrrhenian sea, stretching from the mouth of the river Magra to that of the river Volturno, were up to within comparatively recent times uninhabitable because of the marked prevalence of malaria. Systems of drainage and filling in have now made this region habitable and converted it into a rich and fertile area. In Dante's time these marshes represented an absolute waste; no less desolate than the region about the Lake of Bolsena. What stench must have been ereated in the hospital wards, such as they were, where coction or suppuration was above all things promoted in the treatment of wounds and other surgical lesions! Of interest is the following reference. Dante, who is to mount upon the back of Geryon, becomes unnerved,

Such as he is who has so near the ague
Of quartan that his nails are blue already,
And trembles all, but looking at the shade. (Inf. XVII, 85.)

Very probably the chills and rigors characteristic of the cold stage in malaria are here thought of. However the term, *quartan*, most usually applied to one form of malaria in the present day, had in Dante's age a more general and wider application. The classification of fevers in vogue then being into semitertians, tertians, quartans, quintans, septans and nonans. The prognosis depended much upon whether these were intermittent or protracted, whether diurnal or nocturnal. The quartan fever was considered as not only free from evil consequences but even favorably, in that it was thought to often carry off other diseases with which the patient suffered.

The following lines intimate Dante's keen powers of observation and are of interest in their medical allusion. He sees a spirit stung by a serpent; the spirit looked at his aggressor,

*** * * but said naught;**
Nay, rather with feet motionless he yawned,
Just as if sleep or fever had assailed him. (Inf. XXV, 88.)

Dante probably gleaned this from observing the lassitude and desire to yawn and stretch which is so commonly felt at the onset of intermittent fevers and particularly so in the first stage of malarial paroxysms.

In the tenth gulf of Hell, Dante is held fascinated by a dispute and wrangle between two sinners, Adam of Brescia, a counterfitter, and Sinon, the Greek, who persuaded the Trojans to accept the wooden horse. Of the former we are given this description:

I saw one made in fashion of a lute,
If he had only had the groin cut off
Just at the point at which a man is forked.
The heavy dropsy, that so disproportions
The limbs with humors, which it ill concocts,
That the face corresponds not to the belly,
Compelled him so to hold his lips apart
As does the hectic, who because of thirst
One tow'rds the chin, the other upward turns. (Inf. XXX, 49.)

Adam confides to Dante his craving for a drop of water and tells him that his memory of verdant streams dries him up more

Than the disease which strips my face of flesh.
(Inf. XXX, 70.)

So heavy is he with his dropsy that in a hundred years he can not move an inch. Upon request of Dante, Adam gives information of his neighbor, Sinon of Troy, who is smoking as "a wet hand does in winter," and who reeks with acute fever. Sinon becomes angered at Adam for the account given Dante of him, and to avenge this strikes Adam

* * * with the fist upon his hardened paunch
It gave a sound as if it were a drum. (Inf. XXX, 102.)

Adam retaliates by striking Sinon in the face "that did not seem less hard," than Adam's paunch. An altercation between these two then follows, in which Sinon addresses Adam with

"And rueful be it to thee the whole world knows it."
"Rueful to thee the thirst be where with cracks
Thy tongue," the Greek said, "and the putrid water
That hedges so thy paunch before thine eyes." (Inf. XXX, 119.)

To which the false coiner makes reply,

* * * * * "So is gaping wide
Thy mouth for speaking evil, as 't is wont;
Because if I have thirst and humor[5] stuff me,
Thou hast the burning and the head that aches,
And to lick up the mirror of Narcissus
Thou wouldst not want words many to invite thee."
(Inf. XXX, 125.)

To diagnose the disease with which Dante would have us know Adam is afflicted may appear to be of idle purpose; but granting permission to speculate, the heavy dropsy, the wasted features may be assumed to conform to the ascites and facies met with in hepatic cirrhosis. And the hectic, with cracked tongue longing for water, with a paunch that when struck sounds like a drum, and again the facial expression (Hippocratic faeics), brings to mind general peritonitis, for it is common to see these both in one, and the patient down with hepatic cirrhosis dies of secondary peritonitis. Dante's remark, applied to Sinon, whom he saw "smoking like unto a wet hand in winter," is probably learned from Hippocrates. Francis Adams' translation of Hippocrates' treatise on Airs contains the following remarks: "A common fever (epidemic) therefore is such because all draw in the same breath (pneuma)." Hippocrates afterwards attempts an explanation of the phenomena of rigors, which, however is not very intelligible, and then of the febrile heat and *sweats* which succeed them. The latter he compares to the "condensed steam of boiling water." The views concerning dropsy current in Dante's day were largely those of Hippocrates and Galen, their opinions being the code taught. Hippocrates held that there were "two kinds of dropsy, the one anasarca, which when formed is incurable, the other is accompanied with emphysema (tympanites?) and requires much good fortune to enable one to triumph over it." Galen's commentary on this informs us that in place of two dropsies there are three at least, meaning by these, anasarca, aseites and tympanites. A like opinion is given by Paulus Ægineta.

The following reference seems in its medical affirmation almost as if spoken by a physician. Dante meets with the spirits punished for soothsaying. They, because they sought to see before them and foretell things, are made to look and move backwards. Dante sees some who

Wondrously * * * seemed * * * distorted,
From chin to the beginning of the chest;
For tow'rds the reins the countenance was turned,

[5] Moisture.

And backward it behooved them to advance,
As to look forward had been taken from them.
Perchance indeed by violence of palsy
Some one has been thus wholly turned awry;
But I ne'er saw it, nor believe it can be. (Inf. XIX, 11.)

The physicians worthy of mention in the Divine Comedy we can dismiss with a few remarks, for in accordance with the nature of the poem they are given no opportunity to practice their art. For the same reason also we meet with a total absence of any reference to therapeutics. The physicians for the most part are but mentioned by name and grouped with other spirits in interesting assemblages and, like all of Dante's characters, are presented merely as representative types. Dante entering the first circle of the Inferno, the Limbo, where are those virtuous but unbaptised, finds among the spirits there

Galen, Hippocrates and Avicenna,
Averroes who the great Comment made. (Inf. IV, 143.)

In their circle also,

Of qualities I saw the good collector,
Hight Dioscorides. * * * * (Inf. IV, 140.)

Associated with these are the philosophers and other great spirits, the master of this throng,

All gaze upon him and all do him honor. (Inf. IV, 133.)

is Aristotle. Of these Hippocrates, Averroes and Aristotle receive further mention in the Comedy. In an allusion which Dante makes to the pursuit of worldly things instead of Divine, he mentions Taddeo, as type representative of those following the former. A like allusion is found in the line

One after laws and one to aphorisms. (Par. XI, 4.)

Here undoubtedly Dante refers to the well-known Aphorisms of Hippocrates.

Whether or not Dante knew these masters by their works need not concern us, though it is fair to assume that he did, at least in part and his many commentators appear to concede this, especially on the ground that to join the guild of physicians and apothecaries some knowledge of medicine must have been his as a prerequisite.

To the medical student these names are familiar. Aristotle, Hippocrates and Galen are too well known to require any comment, excepting perhaps that Aristotle came in contact with medicine really only through his physiology and his researches in the field of comparative anatomy.

Avicenna (980-1037), surnamed by the Arabs, the Prince of Physicians, enjoyed, next to Galen, the greatest authority in the medical world of the Middle Ages. The author of some hundred and five known writings, his *Canon Medicinæ,* a system of medicine in five books, was the text and law in medical art and in its Latin translation served this purpose as late as the seventeenth century. His reputation heightened by the nullity of his time, was gained more through his technical abilities and high cast positions than by his scientific accomplishments. His works were largely mere compilations.

Dioscorides' (40-90) fame rests upon his materia medica, which work endured throughout the Middle Age as the main text-book on this subject. He is said to have recognized some four hundred plants. From among his medicines some are given place in the pharmacopeias of today, among others, castor oil, cinnamon, fern and aloes.

Averroës (1126-1148), like Aristotle, philosopher rather than physician, translated the writings of the latter into Arabic from which tongue they were rendered into Latin, first, it is stated, in 1472. His writings are of interest to the physician in that they have supplied numerous commentaries to those of Aristotle, treating on medical subjects, and in opposing many of Galen's views. The writings of the authors mentioned were those most extensively employed as texts in medicine in the time of Dante; from them the profesors in medicine read to their classes, explaining, translating and making compendiums from and comments to them.

Thaddaeus, of Florence (1215-1295 (1303)) was a contemporary of Dante. He held a professorship in medicine in Bologna. Through his efforts the practical introduction of Arabic sciences into the medical schools of Italy was largely due. He is also generally accredited as being the first known medieval writer who assayed in good faith and with excellent judgment, to unite the philosophy of the age with rational medicine. From his professional career resulted the translation of Aristotle, commended by Dante in the *Convito,* and his comments on the Aphorisms and Prognostications of Hippocrates and Galen. He is mentioned by the early commentators of Dante as having been the most skilled physician of his age and in originality equal to Hippocrates. Dante's choice of him as a representative of those engaged in pursuit of worldly things may rest upon the quoted fact that Thaddaeus was notorius for his exorbitant fees and his covetousness. We are told that in 1285 he asked three thousand Bolognese lires and an escort to and from the place for his services in attending an Italian nobleman.

We might add to this list of physicians the names of some who while not referred to by Dante as such, yet deserve recognition from the medical student. From among the ancients to whom Dante gives a place in the Divine Comedy we may select, Thales of Miletus, Anaxagoras, Empedocles (to whom we owe the terms amnion and chorion), Heraclitus, Democritus, Epicurus and Zeno. These philosophers were metaphysicians and physicists (natural philosophers) as well, and in those capacities exercised a very essential influence upon Greek medicine. The philosophers of the Middle Ages, who busied themselves incidentally with medicine, that being a branch of medieval philosophy, are represented by Albertus Magnus, Thomas Aquinas, Hugo de St. Victaire and Peter of Spain. The opinions of Albertus Magnus and Thomas Aquinas exercised a most profound influence upon the medicine and the natural sciences generally during the entire Middle Ages following the period in which they lived.

Considered by themselves, the medical references in the Divine Comedy give no reliable index from which to form an opinion of Dante's medical knowledge. True some few give evidence that Dante was not a stranger in this art, and that without doubt he gleaned also from observation, yet we can ill afford to claim these as the product of a mind especially trained in medicine. For the most part the references are popular and general and at best tend to give but a partial reflection of the medicine current in Dante's time. As we read it in the Divine Comedy it is the medicine of Hippocrates and Galen, with a touch of the Arabic, and interwoven with theology and mysticism. Whether what it expresses was Dante's belief we can not decide. Dante may have believed with some of the ablest minds of his day in the virtue of gems and amulets, in magic and in the healing powers of the saints and the evil workings of the devil, or he may have shared these beliefs as little as we do today. His age professed such beliefs and he may have availed himself of its creed in medicine, as in other things, the better to induce appreciation of his poem, for he intended it to be read by all men and therefore wrote it in the "vulgar" tongue. The medicine in Homer, Shakespeare or Goethe has not proved these authors to have been physicians, neither can that of the Divine Comedy or for that matter, that in any of Dante's writings make out Dante a physician. The truth is, that it was only as a poet that Dante was great and original, and whether physician or not, he did not intend to convey his knowledge of medicine to us, but drew upon it merely as he did upon all those branches of science and art with which his genius and wide range of learning had acquainted him to contribute their share in the making of the pillars of that enduring superstructure the Divine Comedy, the ineffaceable mirror of the Dantean Age.

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It would require a very large volume to contain nothing more than the names of almost innumerable particular and special students of and treatises that have been published on the Divine Comedy. I doubt not that more than one dissertation on the medicine in the Divine Comedy may be found amongst the literature of different nations, if it were sought for amongst the hundreds of books and thousands of pamphlets. I have made no effort to find one. I have availed myself of and borrowed freely from many books, deemed reliable sources treating on the life of Dante, on the history of medicine and the history of that age. A few of those I have found most helpful are here added.

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MOLIÈRE AND THE PHYSICIAN.

By Max Kahn, M. A., M. D., New York.

Boileau, the brilliant and outspoken critic of the French Elizabethan Era, in a conversation with Louis XIV, informed the *Grand Monarque* that he considered Molière the greatest of French writers, whereat Louis the Great sneered. It was this same critic, who, on being asked his opinion of some stanzas written by the King, cleverly replied: "Sire, in all things are you successful. You had desired to write the worst poem in the world, and you have admirably fulfilled your wish." We know not what the scion of the Bourbons retorted, nor how he felt. That he took it coolly is really praiseworthy. It is no wonder that the French king, although he always felt a kindness for the great humorist, disagreed with Boileau. The son of an upholsterer, the man who so inimitably strutted on the stage personifying ludicrous personages, could not, in the opinion of Louis XIV, be the greatest *littérateur* in France.

Not only this monarch, but many wise men in later times, took issue with Boileau. Corneille, Racine, La Fontaine, La Rochefoucauld have all been given precedence over the man who has made the whole world laugh for several centuries. During life Molière suffered intensely from lack of appreciation by the populace and the nobility. Every courtier behaved superciliously toward the cleverest man in the court. He was very poor. Twice he was imprisoned because of lack of funds for the payment of certain debts that were incurred in his attempts to organize a theatre. The clergy were openly against him. The faculty of medicine was silent, because of impotency. At death he was refused consecrated burial, and only a mandate from Louis XIV secured for him religious rites at his funeral. He was interred on a rainy day. The beadle or sexton forgot to mark the grave wherein Molière was laid, so that even the last resting place of the greatest of French dramatists is not known.

All the sciences were at first feared and opposed. So was medicine. What we do not understand, we fear or ridicule. The physician as the expounder of the mysterious science of medicine has, in all ages, caused fear in the timid and has been the butt of criticism from the skeptics. Only a few who have understood have given the physician and his art their just honor and respect.

Molière was not of these. He understood, I firmly believe, the true value of medicine, but he was disgusted with the practice of it in the seventeenth century. When science is degraded to quackery, and when the physician pursues the methods of the charlatan, there is certain to arise a violent opposition to such flagrant ignorance and dishonesty. The dramas "Monsieur de Pourceaugnac," "The Flying Physician," "The Doctor in Spite of Himself," and "The Doctor in Love" were the direct outcome of a healthy dissatisfaction with a profession whose only claim to efficacy was that it had not changed since the days of Hippocrates and Galen, and which took more pride in black gowns and Latin gibberish than in diagnosis and prognosis. When it is said that Molière was feared by churchmen and physicians one has said enough against the reputation of the physicians of those days. A man who was so logical as to be against the clergy of the seventeenth century must have had enough cause for opposing the medical faculty of the time.

Jean Baptiste Poquelin was born in Paris in the month of January, 1622, six years after the death of the world's greatest dramatist in Stratford-upon-Avon. His father was an industrious and thrifty upholsterer. That the Poquelin family was well-to-do is to be seen from the inventory given in the will of Jean Baptiste's mother. She bequeathed silverware and goldware and certain diamonds to the members of her family, and left each of her children an inheritance of five thousand livres. The story extant that the future dramatist suffered from the tight-fistedness of his father is improbable. Doubtless his father with the usual bourgeois respect for gold, was dissatisfied with the tastes of his son. Nevertheless, he paid his son's debts and saw to it that the boy received an education above that of the average lad of the period.

When yet a boy, Jean Baptiste found his father's trade distasteful. The attraction of the streets, where gay things were to be seen, was more to him than the disgusting monotony of the upholsterer's shop, where success depended upon orderliness, punctuality and lacquey-like fawning upon noble customers. Molière was never punctual nor strictly orderly, and certainly he never could toady, and lacking these qualities there was naught in his ancestor's business to please him. The smell of glue in his father's shop could not satisfy the poet who loved the odors of sweet smelling flowers and the beauty of the fields and the sunshine and the forests.

The streets of Paris, though very narrow and very dirty in those days, were quite gay. Swashbuckling musketeers haughtily strutted about and were very happy in provoking duels. They fought for insults to the king or their regiment, or to prove the superiority of certain sweethearts, or for the

honor of chastising peasants. It is said that the redoubtable Cyrano de Bergerac, whom Rostand has made the hero of his best drama, fought a dozen times and killed ten adversaries in order to defend the honor of his own elephantine proboscis. Grisettes, wenches and quacks traversed all the thoroughfares, and accosted all passers-by who seemed capable of spending some sous. In certain main streets, it was especially interesting. In the rue de Pont Neuf, the comedians of the day used to perform for the benefit of the public. Here young Jean Baptiste was Bellerose and Mondory and Gros Guillaume, all famous artists of that time, who set the audiences roaring at their coarse jests and phantastic contortions. Here, also, he saw Guillot Gorju, the actor quack, who ridiculed *les médecins,* and whose sharp witticisms Molière incorporated later into his dramas.

At the age of fourteen Molière was sent to the Jesuit College at Clermont near Paris, where he associated with sons of the nobility. Here he undoubtedly saw Prince Armand de Conti who later became his patron. There is no evidence, however, that this prince ever so much as talked to the low born Poquelin. Little else is known of Molière's student life. He studied for some time under Gassendi. He especially admired Lucretius and Terence among the ancients and Rabelais among the moderns. He left the above named institution, after a course of study of several years, for the law school at Orleans, "where," as his enemy Le Boulanger de Chalussay has it, "any donkey could buy a diploma." However, he went to the law courts only once.

A tradition would have it that Molière studied for the priesthood, but this is wholly a fable, for the bright-witted, free-willed Molière could never brook a monkish life with its restrictions and monotony. Still, if he ever did intend to practice law or study theology, the purpose must have been more desultory than serious, for we find him in the month of January, 1643, fully embarked on the venturesome career of comedian and stage manager. (Chatfield-Taylor: Life of Molière.)

Travelling, actor-like, he fell in with the Béjart family, a strolling band of performers, and soon ingratiated himself in favor of Madeline Béjart whom he married. Aided by his sweetheart and the whole company, he opened "The Illustrious Theatre." This venture was a failure, and after being imprisoned twice for debt, Molière had to flee Paris to escape another incarceration in the debtor's jail. Together with his company he strolled over France and appeared in Bordeaux, Toulouse, Lyons, Orleans, Limoges, Narbonne and Pézenas at different periods, everywhere receiving permission to erect a stage to perform comedies.

Successively under the patronage of Duke D'Epernon and Prince de Conti, the fortunes of the poet began to flourish. In the provinces and in the capitol, Molière kept his eyes open and he himself began to ridicule the foibles and vanities of the average Parisian bourgeois. Soon dramatic works followed one another, and his fame reached the ears of the king, who from this time forward was quite a generous patron. During this period he wrote his greatest dramas, and, receiving protection from the king, he attacked the medical profession and medicine in general, with so much bitterness that as he had anticipated, the doctors refused to attend him in his last illness. He died on the seventeenth of February, 1673. "This same day, about ten o'clock at night, after the comedy, Monsieur de Molière died in his house, rue de Richelieu. He had played the part of the said *malade* (*Le Malade Imaginaire*) suffering from cold and inflammation which caused a violent cough. In the violence of the cough he burst a vessel in his body, and did not live more than half an hour or three-quarters after the bursting of the vessel." (La Grange: Register.)

To fully comprehend the causes that led Molière to wage a bitter warfare against medicine and the doctors, we must briefly review the medical history of the seventeenth century. Periods in which transpire changes from the accepted state of events and things are ever characterized by violence, satire and much bitterness. The seventeenth century is the transition era from mediæval irrationality and empiricism in medicine to modern scientific experimentation and rationality. In times of revolution, there are ultra-conservatives and ultra-radicals. The medical iconoclasts of the reign of Louis XIV were opposed by the unreasoning obstinacy of the Parisian medical faculty, who thought it a crime to venture out of the rut of prescribed practice. "Who shall judge when doctors disagree," is an old apothegm. The layman becomes puzzled and consults the quack, and the more strife and contention there is between the various schools of medicine, the more will quackery and dishonesty thrive. Between the violent radical and the obdurate conservative, the enlightened cool headed physician is lost sight of.

The practice of medicine in the seventeenth century was mere empiricism. The faculty was inculcated with the dignity of its profession, and laid much stress on the ceremonials of practice. The oath that a professor of medicine took when nominated is quite characteristic: "I here pronounce faithfully to teach in a long gown with wide sleeves, a doctoral cap on my head, a knot of scarlet ribbon on my shoulder." Nevertheless an epoch which could produce such men as Harvey, Sydenham, Malpighi, Willis and many other famous doctors whose names are almost household words, cannot be looked upon as a period of grotesque hypocrisy and profound ignorance. There must be another side to the matter, and the legend of the satirist must not be wholly taken for granted:

Longue peruque, habit grotesque,
Affecter un air pédantesque,
Cracher du grec et du latin,
Tout cela réuni fait presque,
Ce qu'on appelle un médecin.

Molière has tremendously exaggerated in the humorous episodes and the comic situations the true condition of his time. Disgusted as he was with science that was unable to cure his disease, (because no science could cure it), he sought aid amongst the quacks of the Pont Neuf; he consulted the town criers and the wandering mountebanks. If we examine the lives and works of leading physicians of Paris of the seventeenth century, we must inevitably come to the conclusion that

Molière's doctors, the Tomès, Desfonandrès, Macrotons, Bahis are mere burlesques. That they have survived such a long period is due to the fact that they are comical even if not true, and that in their conversation and behavior grains of realism may be discovered.

Molière was very well acquainted with the physicians of the court. Fagon was at that time the chief physician in attendance on the king, a position of great dignity and importance. Fagon occupied the chair of Botany in the *Jardin Royal,* and it was his endeavors and studies that added importance to the science of botany. He corresponded with the learned men of the whole world, and received from them rare botanical specimens which he stored in the *Jardin Royal,* making that institution the most famous museum in Europe. In the year 1665 he made the first catalog of this collection under the title of *Hortus Regius.* He was a most honest man. "His disinterestedness," says M. Fauvelle, "was as wonderful as his learning. He abolished the buying of offices in the learned colleges, and refused large sums of money that were offered him. His modesty was very great, and he always sought to avoid the honors that the faculty desired to confer on him. Compulsion was exerted to persuade him to accept his nomination to the *Academie des Sciences.*"

Dr. Fagon's co-worker was Armand de Mauvillain, the friend of Molière. de Mauvillain was a physician of the Montpellier school, and, therefore, an enemy of the Parisian faculty. It has been surmised that this doctor gave a helping hand to Molière in writing the satires on Medicine. Receiving the degree in medicine from the University of Paris in 1648, he settled in the capital and had quite a lucrative practice. With the advance of the teachings of Harvey and Malpighi, he became an adherent of the theory of the circulation of the blood. de Mauvillain was very learned and very liberal, and the conservatives considered him the anti-Christ of medicine. "If he did not resemble the physicians in Molière's dramas," says Professor Funck-Brentano, "it was because he was Molière's physician himself; and this is enough ground for believing that de Mauvillian, powdered and perfumed as he was, served and abetted his poet friend in order to ridicule his beloved colleagues of the faculty." (Funck-Brentano: Die Ærzte Molières.)

The Parisian college was against all modernism. Like the Chinese, the doctors had built a wall of stone and adamant against the ingress of advanced thought. As Dr. M. J. Conklin remarks, the spirit of the times is happily shown in the following extract from the statutes of the Academy at Helmstadt:

> We desire the medical art, even as it was rightly and wholly fixed and handed down, under the guidance of God, by the artists Hippocrates, Galen and Avicenna, to be preserved and diffused by teaching. We recommend that all Empirics and the 'Tetralogies' of Paracelsus, with other corruptions of medicine not agreeable to the doctrines of Galen and Avicenne, be banished entirely from the academy.

This doctrine was a stumbling block to the progress of all science.

In the reigns of Francis II, Charles IX, Henry III, and Henry IV, the faculty was bitterly embroiled with Ambroise Paré. As Mr. Stephen Paget says "it was a sort of Holy War for the deliverance of surgery from the bondage of medicine."

In the year 1575 (April 22), Paré published his book, a folio of 945 pages, on surgery. It was written in French, so that even a plain mortal (one not begowned or becapped) could understand every word of it. The Faculty became alarmed. On July 9 of the same year, they met and besides observing that Paré was only a barber surgeon, thrust amongst them by the king, ignorant of Latin and Greek, they charged him with gross indecency and immorality. Five days later, Parliament called the case for hearing, and carrying the farce to the end, decided that Paré had no legal right to publish a work on medicine without first receiving permission from the faculty. The defence of the eminent surgeon was quite a shaft of sarcasm against ignorant intolerance:

> For more than thirty years I have been printing my treatises on surgery . . . . which made me think, if I gathered them together, I should be doing a thing very agreeable to the public. Having accomplished it, and that at an expense past thinking—lo and behold—the physicians and the surgeons have set themselves to obscure and suppress them, for this sole reason, that I wrote in our mother tongue, in phrases quite easy to be understood. The physicians feared lest all who should get the book into their hands would be advised how to take care of themselves in time of sickness, and would not be at the pains to call them in. The surgeons were afraid lest the barbers, reading these, my works, would receive full instruction in all the operations of surgery, and would come to be as good as themselves and thus trespass on their domains.

When Paré planned to publish his *second* edition, he consulted the faculty, and in order to please them, he removed his obnoxious articles on fevers (which only physicians could write about) and included his observations on that subject in his discussion of tumors. This modesty and meekness pleased the "congregated college," and they did not oppose the publication of this work. (S. Paget: Ambroise Paré and His Times.)

The faculty in the time of Louis XIV was the same in aspirations and ideas as the faculty in the times of the last Valois. Surgery was opposed because no dignified physician would hold a knife in his hand, and to elevate the barber to the dignity of a doctor was not to be thought of. Circulation of the blood was proscribed because it was English. If the blood did circulate it was against the laws of the faculty. It had no business to flow contrary to the beliefs of Hippocrates and Galen. "Besides," said they, "if the blood circulates, it is useless to bleed, because the loss sustained by an organ will be immediately repaired, hence bleeding is useless, therefore the blood does not circulate."

The prescribing of antimony was prohibited by the faculty at Paris, for the simple reason that the faculty of Montpellier highly recommended it. de Mauvillain espoused the cause of antimony and circulation of the blood and was, therefore, ostracized from the association of physicians.

As strict partisans of the principles of the Parisian faculty, Jean Riolan (1577-1657) and Guy Patin (1601-1672), stand preëminent. Patin, "polemical medical man and clever humorist of that day," said of Riolan that he would rather

give up a friend than an assertion. They were strict adherents of the Iatro-chemical school, founded by Sylvius, "which like other systems, might rather be called a systemic phantasy." This system is based upon the elements of chemistry—the improved successor of alchemy and the first step toward true chemistry—; upon the new knowledge of the circulation of the blood; and upon the closer acquaintance with the chyle and lymph vessels (which had been acquired in this period), as well as upon the old doctrine of the "spiritus and the calor innatus" of the heart. His system, although its author always professes to accept only "experience by means of the senses, is constructed far less upon experience than upon false conclusions drawn from experimental observations, whose connection with his theory is on the whole arbitrary and forced." (J. H. Baas: Geschichte der Medicin.)

Opposed to their beliefs were the theories of the Iatro-mathematical school whose motto was, "In your practice, concern not yourselves with theories." The originator of this system was Santorio Santoro (1561-1636), Professor in Padua and Venice. Their idea was to treat all things with precision, and that all functions in the body were physical rather than chemical. "Thus digestion was referred to as a process of mechanical trituration, and the absorption of chyle was explained as due to the pressure arising from the action of the intestinal movements upon the comminuted food. In a similar way the secretions were referred to as the resistance created by the corners, curves, angles, etc., of the vascular system, and so on."

Guy Patin was a learned man, a brilliant writer and thoroughly acquainted with the Latin language, which he wrote to perfection. "His creed contained but two articles—bleeding and purging with Senna." Certainly he was not a quack, but with mediæval intolerance he opposed all who were against the existing order of things. It might have been of him that Molière has said "that a dead man is only a dead man, and is of no consequence, but a neglected formality does great harm to the entire profession." Guy Patin strongly believed in having his patients die "according to rule rather than to recover in violation of it."

Molière ridiculed all physicians and all medicine. He had no more respect for the "outside doctor"—him of Montpellier—than he had for the members of the Parisian faculty. He was especially venomous against the medical profession because of their seeming ignorance and lack of skill. Suffering as he did from a painful disease he became morose and disgusted with the futility of prescriptions. Whether it was aneurysm of the aorta or pulmonary tuberculosis, as has been surmised by some, in any case, accompanied as it was by hypochondriasis, it was sufficient to especially interest him in the medical factions of his day. He ridiculed all of them impartially.

Molière's dramas against medicine began in his "barn storming" days. "The Flying Physician" and "The Physician in Love" are two plays of inferior quality written by the dramatist at the very beginning of his career. The latter drama is lost. In *Le Médecin Volant* we find Molière's first attack on medicine. Sganarelle, the famous rogue, undertakes to impersonate a learned physician, in order to aid his master in his love affair. He assumes the doctor's gown and talks with the pedantic air, which Molière thought was characteristic of the physician:

> Hippocrates says, and Galen, by undoubted arguments, demonstrates that a person is not in good health when he is ill. You are wise to place all your hope in me; for I am the greatest, the noblest, the most learned physician in vegetable, sensitive and mineral faculty.

Unlike other physicians he not only looks at the urine but also tastes it, but like them he is a stickler for formality. Upon being told his patient is dying, he exclaimed:

> Ah! let her be careful not to do so; she must not amuse herself by allowing herself to die without a prescription from the doctor.

This last remark, the author was very fond of repeating, and we find it again in 'The Physician in Spite of Himself.'"

In another of his farces "The Jealousy of Le Barbouillé" written during his provincial career the doctor is still more ridiculed. Le Barbouillé is plagued by a shrewish wife, who, as fate would have it, always gets the upper hand of him. The unfortunate husband seeks advice from a doctor, and like a good business man, accosts the physician and immediately comes to the point:

Le B: "I desire to beg for an opinion on a question of great importance to me."

The doctor, ever wakeful to the danger of losing his dignity, replies in what he endeavors to make a very reproving statement:

> You must be very ill bred, very loutish and very badly taught, to speak to me in that fashion, without first taking off your hat, without observing *rationem loci, temporis et personæ*. What! You begin by an abrupt speech, instead of saying *Salve, vel salvus sis, doctor doctorum eruditissime*. What do you take me for, eh?

No apologies will help. In endeavoring to excuse himself, poor Le Barbouillé gets more entangled. What astounds him most is that the doctor does not care for money. "Well, I made a mistake," he soliloquizes puzzled. "Seeing him dressed as a doctor, I felt that of necessity I must speak of money to him, but since he does not want any, nothing can be more easy than to satisfy him." The doctor is a very verbose individual who is continually advising his hearers to be brief. The stage direction in the seventh scene is interesting:

> All wish to explain the cause of the quarrel: The doctor explains that peace is a fine thing. They all talk together, and make a dreadful noise. In the midst of all this Le Barbouillé ties the doctor by the legs with a rope, throws him down on his back, and drags him away. The doctor goes on talking all the time, and counts all his arguments on his fingers, as if he were not on the ground.

Molière took a general interest in the educational affairs of France. In *Le Marriage Forcé* he throws a shaft at the University of Paris, which was endeavoring to persuade Parliament to confirm a sentence dated Sept. 4, 1624, which condemned to death all those who would dare to attack the Aristotelian doctrine.

Sganarelle meets two philosophers discussing and quarrelling. He accosts one, and is met with gibberish that he does

not understand. "Devil take the scholars," he exelaims. "They will never listen to anybody. I see it was the truth I was told and that this Master Aristotle was a talker, and nothing else."

The doctor has a very good opinion of himself.

Get along, you are more impertinent than the fellow who maintained that we ought to say the *form* of a hat instead of a *figure*, and I will prove it to you at this time, by the help of demonstrative and convincing reasons, and by arguments *in Barbara*, that you are and never will be anything but a simpleton and that I am and ever shall be, *in utroque jure*, the Doctor Pancrace. . . . A man of sufficiency, a man of capacity, a man finished in all the sciences, natural, moral, and political. A savant, savantissime, *per omnes modos et casus*. A man who has a knowledge suptrlative of fables, mythologies, and histories; grammar, poetry, rhetoric, dialectics, and sophistry; mathematics, arithmetic, optics, ornicritics, physics and metaphysics; cosmometry, geometry, architecture, speculary, and speculatory sciences, medicine, astronomy, astrology, physiognomy, meteposcopy, chromancy, geomancy.

The doctor gets out of breath naming all these true and pseudo branches of learning. He is very intolerant of a diverse opinion, and would condemn anyone to the galleys or scaffold for contradicting him.

Molière ever attacks vice, undauntedly, uncompromisingly. He seems to fear to be too lenient with corruptions, lest he himself become indifferent. Pope well puts it:

> Vice is a monster of such frightful mien,
> That to be hated needs but to be seen,
> Yet seen too oft, familiar with her face
> We first endure, then pity, then embrace.
>
> —*Essay on Man.*

Not all the doctors of Molière are so indifferent in money matters as is the savant Pancrace of *Le Marriage Forcé*. In fact, the humorist rarely imagined a physician who was not absorbed in money making. He is not harsh with weaklings and sinners. He laughs at them heartily, and he expects us not to condemn his Sganarelles and Gros-Renés and Mascarilles. It is true that they are deep-dyed rogues but he smiles at their escapades and is very lenient with their delinquencies. Not so with the physicians and savants. There always seems to be something rankling in his heart against these learned men. He considered them hypocrites, fools, and villains. Humorist though he was, he never kept his sense of humor in dealing with doctors. Molière's suave and witty testimony cannot be accepted before a court of justice. Molière does not bear true witness.

Critics and editors of Molière always feel themselves called upon to defend the dramatist for his attacks on the doctors. Mr. Chatfield-Taylor in his admirable biography devotes a whole chapter to the strife between Molière and the faculty, and he covertly sneers at the College of Medicine, who, when they congregated, resembled more an assembly of Roman Senators than a meeting of French scientists. Professor Charles Heron Wall in his introduction to *Monsieur de Pourceaugnac* finds it necessary to state that "the attacks upon the doctors are not exaggerated." In their endeavor to defend the critics become partial and unjust.

Monsieur de Pourceaugnac is perhaps the best farce ever written, and Molière did not feel called upon to do anything but cause uproarious laughter. He does not attempt to amuse us with the sharp witticism of the comedian; instead, he employs the broad humor and crude jests of the clown.

M. de Pourceaugnac, a lawyer from Limoges, has come to Paris to marry Julia the daughter of Oronte. He is unacquainted with Paris and is easily led astray. Julia does not feel inclined to obey her father, and her affections are centered upon Eraste, a young fashionable gentleman. In order to circumvent the meeting between Pourceaugnac and Oronte, Serigani the servant of Éraste persuades the unfortunate countryman to place reliance on Éraste and himself. Unsuspecting, he is conducted to two physicians, who readily believe Serigani that Pourceaugnac is insane, and ignoring the wretched man's protestations, they argue and debate in their usual pedantic style over the malady of their patient. The consultation between the doctors is extremely witty. After the senior physician has given a very lengthy and laughingly learned discussion of the case, the junior doctor, in rapt admiration, replies:

Heaven forbid, Sir, that it should enter my thoughts to add anything to what you have just been saying. You have discoursed too well on all the signs, symptoms and causes of this gentleman's disease. The arguments you have used are so learned and so delicate that it is impossible that he is not insane and hypochondrically melancholic; or were he not, that he ought to become so, because of the beauty of the things you have spoken and of the justness of your reasoning. Yes, sir, you have graphically depicted, *graphice depinxisti*, everything that appertains to this disease. Nothing can be more learnedly, judiciously and ingeniously conceived, thought, imagined than that you have delivered on the subject of this disease either as regards the diagnostic, the prognostic or the therapeutic, and nothing remains for me to do but to congratulate this gentleman upon falling into your hands. All I should like to add is to let all his bleedings and purgings be of an odd number, *numero deus in pare gaudet.* to take the whey before the bath, and to make him a forehead plaster, in the composition of which there should be salt—salt is the symbol of wisdom.

There is one thing about this comedy that is gratifying to the doctors and this is that Molière as pointedly attacks the lawyers as he does the physicians. In fact, he ridicules the men of law more than he does the practitioners of medicine. They have a refrain which they are constantly reciting:

> Your deed
> Is plain and clear
> And all the gear
> Of wigs and law
> Upon this flaw
> One verdict bear . . . .
> Polygamy's a case, you find,
> A case of hanging.

Only one man who was not a doctor took up arms in defense of the medical faculty. Le Boulanger de Chalussay wrote a comedy entitled *Élomire Hypochondre, ou Les Médecins Vengés* in which he ridiculed Molière (Élomire) and his wife, and represents the doctors as learned men who take vengeance on the mortal who has dared to attack the dignity of the most

ancient and honorable profession. The play produced a great furor, and the conservatives were extravagant in its appreciation.

Unto death Molière despised physicians. His last comedy, *Le Malade Imaginaire,* was written at a time when he was very ill and nearly dying. Molière himself acted the part of Argan, the imaginary invalid. This drama is very laughable. The story is very simple. Argan, the imaginary invalid, is constantly employing a physician to prescribe for him. As his second wife says, "He is a wretch, unpleasant to everybody, of nauseous dirty habits, always a clyster or a dose of physic in his body." His wife pretends great affection and diplomatically so manages affairs that her husband should make his will in her favor, thus dispossessing her step-daughter Angélique. Her plan would have been successful but for Toinette the maid of the intended victim. Argan, desiring to reduce his doctor's bills, hits upon the remarkable scheme of marrying his daughter (who is in love with a young, handsome gentleman) to his physician's son.

The curtain rises upon Argan sitting alone and adding up his apothecary's bill.

> Item, on the 24th, a small insinuative clyster, preparative and gentle, to soften, moisten and refresh the bowels of Mr. Argan—thirty sous.
>
> Item, on the said day in the evening, a julep, hepatic, soporiferous, and somniferous, intended to promote the sleep of Mr. Argan—thirty-five sous.
>
> Item, on the 26th, a carminative clyster to cure the flatulence of Mr. Argan.—thirty sous.

And more, and still more. A goodly list and quite lucrative for the medical man in this case.

When the intended son-in-law, who is to receive his doctor's degree in three days, comes to visit the Argan family, he proves positively that he is invested with great learning. He mistakes the step-mother for Angélique and pays her compliments intended for his belamour. His father, Doctor Diafoirus, is constantly prompting him as to good manners and fashionable etiquette. His father, in praising him, says:

> "In all disputations has he rendered himself formidable, and no debate passes but he goes and argues loudly and to the last extreme on the opposite side. He is firm in dispute, strong as a Turk in his principles, never changes his opinion, and pursues an argument to the last recesses of logic. . . . . But, above all, what pleases me most is his blind attachment to the principles of the ancients, and that he would *never listen* to the pretended discoveries of our century concerning circulation of the blood and other opinions of the same stamp."

In other words, asinine obstinacy is the marked characteristic of the future practitioner. In reading these lines we are reminded of the famous hero of Butler's panegyric on Puritanism. Hudibras, likewise, was strong in debate:

> He was in logic a great critic,
> Profoundly skilled in analytic;
> He could distinguish and divide
> A hair 'twixt south and southwest side;
> On either which he would dispute,
> Confute, change hands, and still confute.
> He'd undertake to prove by force
> Of argument, a man's no horse;
> He's proved a buzzard is no fowl,
> And that a lord may be an owl;
> A calf an alderman, a goose a justice,
> And rooks, committeemen and trustees.
> He'd run in debt by disputation.
> And pay with ratiocination,
> All this in syllogism true,
> In mood and figure, he would do.
> (Hudibras, Part I, Canto I.)

The young doctor is very gallant. He graciously invites his lady-love to amuse herself by assisting at the dissection of a woman upon whose body he is to give lectures; a new and improved method of gratifying the desire for fun in a young girl!

Once M. Argan refuses to take a prescription of his physician. The latter does not seem at all pleased about it:

> What daring boldness; what a strange revolt of a patient against his doctor! . . . . A clyster which I have had the pleasure of composing myself, invented and made up according to all the rules of art. . . . . A case of high treason against the faculty.

The final scene is an interlude representing the admission of a student to the degree of doctor of medicine. The scholars and professors recite a piece composed of dog-Latin and French praising medicine, and in a burlesque manner they march on the stage with clysters and bleeding pails. Their refrain is:

> *Clysterium donare,*
> *Postea seignare,*
> *Ensuita purgare.*

Really not a bad remedy for all diseases.

Like Rabelais before him, Molière always makes us laugh, but more than that he makes us think. Undaunted, he stood alone and battled with those in authority. Their endeavors to harm him proved fruitless and he escaped unscathed. Undoubtedly Molière had great influence upon his contemporaries and we notice great improvement in the proceedings of the Medical Faculty in the early part of the eighteenth century. We should not consider Molière as an enemy of medicine, but as a critic of the ignorance and intolerance of the medical practitioners.

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THE NEW DEPARTMENT IN THE JOHNS HOPKINS UNIVERSITY.

"ART AS APPLIED TO MEDICINE."

By MAX BRÖDEL,
Associate Professor of Art as Applied to Medicine.

The illustrations of medical publications are as a rule far below the standard set by other publications, both in regard to the correctness of the pictures and their artistic merits. In many instances, in fact, medical illustrations do not aid the text, but rather obscure it, and are often crude in the extreme. Illustrations of medical books are a highly specialized form of art, requiring on the part of the artists not only reliable draughtsmanship and adequate technique, but also a thorough understanding of medicine in most of its branches. It is obvious that a medical illustration can never be a success if the artist does not fully comprehend the object which requires illustration. It is hopeless here more than elsewhere in art for an artist to attempt to draw or paint an object of which he has no clear conception. Such a conception is absolutely necessary because it serves to create a picture in the artist's mind which must be the forerunner or model of the actual picture afterwards upon his paper. Upon the clearness of this mental picture depends the scientific as well as the artistic value of the drawing, for only under this condition can the artist's hand work with freedom and precision.

All medical illustrators of the present day are self-taught, because hitherto there has been no school where instruction in this important branch of art could be obtained. Most of them have been compelled to go through a long and tedious period of self-instruction marked by many failures. Their development has for the most part been a process of groping in the dark with an occasional success in the latter part of their career. Some of the best have died without having had an opportunity to train a successor, and the experience they have gained and the methods they have gradually evolved have thus been buried with them. No science, no art can ever develop to a high degree unless a new generation can base its methods upon the work of the last generation and thus profit by the failures and successes of others.

For this reason a department has been created in the Johns Hopkins University to be known under the general title "Art as Applied to Medicine." Its purpose is to bridge over the gap existing between art and medicine, and to train a new generation of artists to illustrate medical journals and books in the future and to spare them the years of trial and disappointment of their self-taught predecessors. In view of the fact that medical illustrating is midway between art and medicine, it is proposed that the instruction given be designed for the needs of two classes: (1) For medical students, and (2) for artists. Experience in the past has taught us that promising pupils can be obtained from both medical students and artists.

The following is the plan according to which the proposed course will be given:

A. COURSES FOR MEDICAL STUDENTS.

1. A course of lectures to first-year class for one hour a week during the first trimester. This course is intended to give general instructions in the elementary principles of drawing and sketching as an aid to the study of medicine.
2. A short course in artistic anatomy to be given during the second trimester. The purpose of this course is to supplement the study of the cadaver in the dissecting room.
3. A course in actual drawing open to students of the four classes, to research workers and to members of the faculty for two hours twice a week throughout the year. This course will be limited to 12 students.

   The work will first deal with the exact study of the plastic representation of medical objects of all kinds. Later on this will lead to the study of diagrammatic drawings and sketches useful in taking medical histories or illustrating lectures with blackboard sketches. Lastly, a suitable technique for making medical illustrations for publication will be taught.
4. Research workers who require pictorial representation of their research will be taught the principles of making such drawings.

B. COURSES FOR ARTISTS AND ART STUDENTS.

1. Special instructions to medical illustrators who desire to take up advanced work in a particular branch. The fee will depend on the length of the course and the character of the instructions. Minimum fee $25.00. Such courses may be taken at any time during the academic year.
2. A regular course for beginners. This course will continue during the entire day throughout the academic year (October 1-May 31).

   Applicants who are not graduates of an art school must submit samples of their art work. The duration of the whole course will of necessity depend on the talent of the individual, the average term, however, not exceding two years. The fee is $100.00 a year.

   Drawings of especial merit may be accepted and utilized by the department for publication and as a practical test of the artist's ability. Although such drawings become the property of the school, the student will receive several printed proofs after publication. All drawings and sketches not so honored will remain the property of the student. The above course will be as follows:

   a. Anatomical studies of the skeleton, muscles and viscera from the standpoint of the medical illustrator. Everything studied is sketched or drawn.
   b. Studies of fresh material at autopsies combined with microscopic studies of the various tissues in health and disease. A number of accessory methods will be employed in studying fresh tissues.
   c. Studies of hardened specimens from the various pathological collections combined with the study of the texture of the individual structures of the body.
   d. Based on the foregoing the student is ready to study the pictorial representation of physical examinations, various kinds of treatment, and the different steps in surgical operations.
   e. Stress will be laid on the correct attitude of the medical illustrator toward problems in medical research and toward the conception of a medical illustration in general as an aid to the text and also as a work of art.
   f. Parallel with and supplementing these studies will be instructions and demonstrations in the various techniques suitable for medical illustrations intended for publication. These are:
      (1) Half-tone drawings in crayon, etc.—Mixed technique.
      (2) Water-color painting.
      (3) Line drawings in pen and ink. Diagrams.
      (4) Charts for class demonstrations.
   g. Studies of the various methods of reproduction from the standpoint of the illustrator.

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THE PROBLEM OF TYPHOID FEVER IN BALTIMORE.

By William W. Ford, M. D., D. P. H.,

Associate Professor of Hygiene and Bacteriology, The Johns Hopkins University.

AND

E. M. Watson, A. M.

(From the Laboratory of Hygiene and Bacteriology, The Johns Hopkins University.)

During the past year the city of Baltimore has suffered from a serious and costly epidemic of typhoid fever. From January 1, 1910, to January 1, 1911, 235 deaths from this disease were reported to the Board of Health, while for the same time the total number of cases equaled 1890. The majority of these cases developed during the summer and autumn months, as is shown on Charts I and II. Up to July 1 but 44 deaths and 193 cases had been found, but beginning with this month the disease began to show a greater prevalence. During July, 7 deaths and 110 cases were reported; during August, 30 deaths and 473 cases; during September, 49 deaths and 398 cases; during October, 42 deaths and 359 cases. The two subsequent months, November and December, showed some falling off in both case incidence and fatality, 37 deaths and 251 cases occurring in November and 26 deaths and 106 cases in December. As the cold weather of 1911 became more settled the cases diminished in number, 55 cases and 11 deaths appearing in January, 31 cases and 3 deaths in February, and but 35 cases and 5 deaths in March.

Chart I.—Typhoid Fever in Baltimore, January, 1910, to June, 1911.

		Case Incidence.	Deaths.			Case Incidence.	Deaths.
1910.	Jan.	39	7	1910.	Oct	359	42
	Feb.	25	11		Nov.	251	37
	Mar.	30	12		Dec.	106	26
	April	22	4	1911.	Jan.	55	11
	May	31	2		Feb.	31	3
	June	46	8		Mar.	35	5
	July	110	7		April	44	8
	Aug.	473	30		May	56	7
	Sept.	398	49				

During the year 1909 there were 136 deaths from typhoid and 1069 cases; during 1908, 180 deaths and 1426 cases; in 1907, 230 deaths and 1417 cases. Thus the year 1910 shows more typhoid fever than does any previous year for a considerable period of time. The number of cases recorded in the Department of Health is the largest since vital statistics have been kept in Baltimore, and the number of deaths is only equalled by the figure for the year 1890, when 247 fatalities from this disease were reported.

The deaths in the summer and autumn months also show a great increase over the corresponding months of last year. In 1909, 20 deaths occurred during August, but in 1910 this

rose to 30. For September the number rose from 24 to 49; for October from 23 to 42; for November from 10 to 37; while in December the deaths rose from 9 to 26, as is shown in Chart III.

CHART II.—Typhoid fever in Baltimore. January, 1910, to June, 1911. Case incidence.

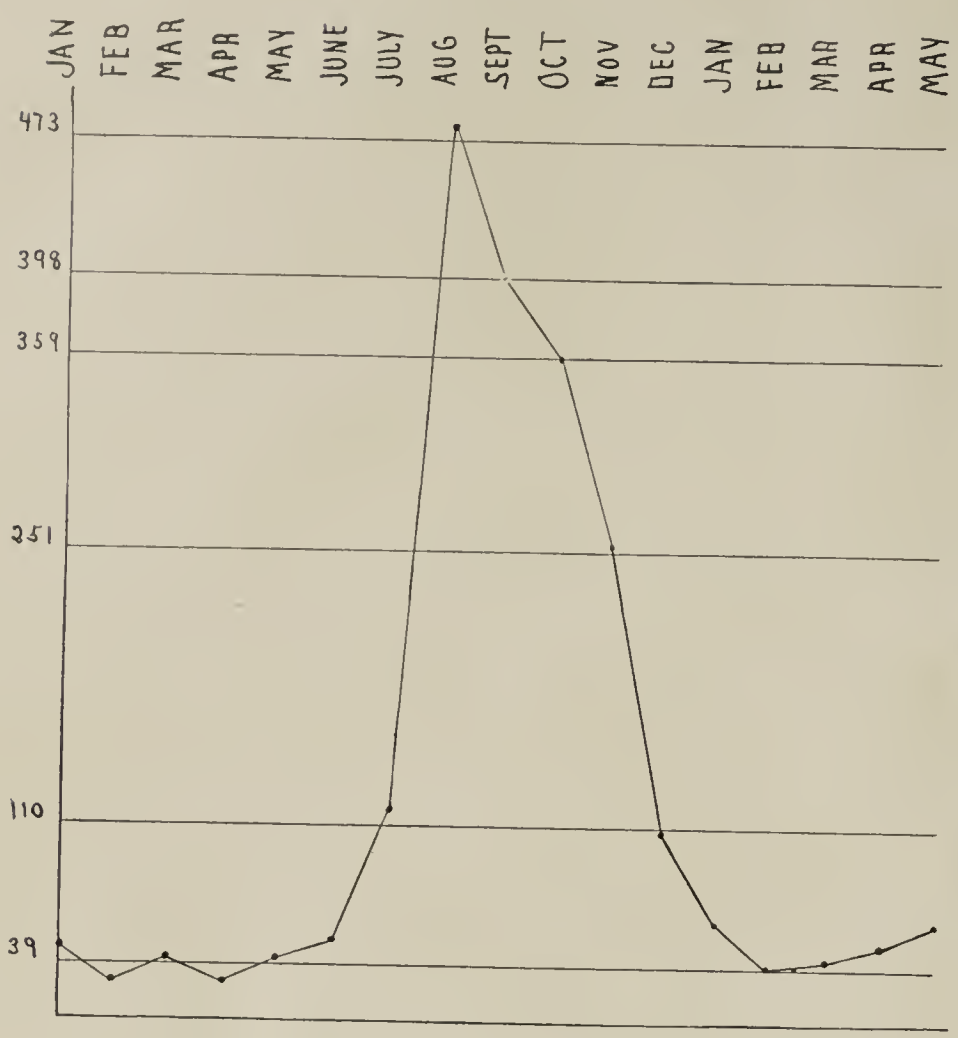
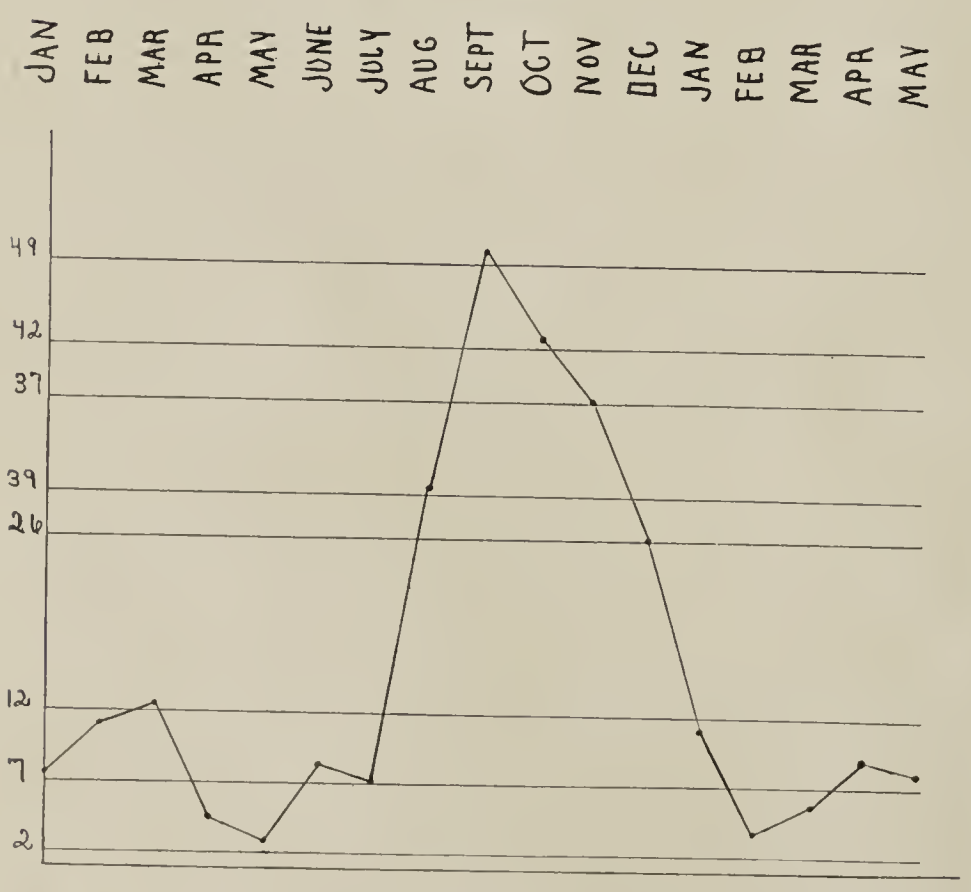


CHART III.—Typhoid fever in Baltimore. January, 1910, to June, 1911. Mortality.



While these figures indicate an increase in typhoid fever during the year just past, compared with preceding years, it must not be supposed that this predominance of the disease in any one particular period has not previously been noted. Thus, in the year 1907 there were 230, and in the year 1902 220 deaths. As can be seen from Chart IV, typhoid fever has always existed in the city of Baltimore. Deaths from it were first reported officially to the Board of Health about the year 1875. At the end of this year 187 deaths were assigned to this cause. Since then statistics of the Department indicate a constant recurrence of the disease from year to year. During the earlier years the diagnosis did not rest upon such secure grounds as at present, the possibility existing that cases of malaria and early tuberculosis might be included among the cases diagnosed as typhoid. Gradually, however, as the symptomatology of the disease became better understood, as the diagnosis of malaria and tuberculosis was more frequently made on the evidence of the parasites and not merely upon the symptoms, and finally as the Widal reaction was introduced, rendering

CHART IV.—Typhoid fever in Baltimore.

Average deaths 1875 to 1880 ..... 183 per year.
Average deaths 1880 to 1885 ..... 167 per year.
Average deaths 1885 to 1890 ..... 162 per year.
Average deaths 1890 to 1895 ..... 207 per year.

Year.	Cases Reported.	Deaths.	Per cent.	Population.
1895	260	173	66.53	479,907
1896	472	188	39.83	493,147
1897	363	189	52.06	506,398
1898	545	189	34.68	541,000
1899	462	153	33.11	541,000
1900	871	189	21.70	541,000
1901	792	141	17.80	518,000
1902	1086	220	20.26	535,000
1903	768	189	24.61	533,000
1904	916	199	21.72	541,000
1905	1019	197	19.33	550,000
1906	1215	183	15.06	558,000
1907	1417	230	16.23	565,000
1908	1426	180	12.62	573,000
1909	1069	136	12.72	581,000
1910	1890	235	12.43	585,000

the recognition of typhoid infection much more certain, the returns made to the Board of Health have become more and more accurate. Despite the fact that some of the cases formerly considered typhoid fever would now be separated from this group, the figures indicate that there has been a gradual diminution in the amount of this disease in the city of Baltimore, as compared with our increasing population. In 1890 we had possibly the largest number of deaths from typhoid ever known here, 247 in an estimated population of 413,000. But since then the number of deaths has diminished annually, the smallest number being reported in 1909, 136 in an estimated population of 580,000.

Beginning with the year 1895 typhoid fever became a notifiable disease in Baltimore, and since then our information has become still more exact. In that year 173 deaths were reported, and 260 cases, a mortality percentage of over 66. The notifications sent to the Board of Health have increased annually, the ratio of death to case incidence constantly falling until in the year 1908 it became 12.62%. That is, during that year

180 deaths from typhoid occurred and 1426 cases were reported. Since the death rate from typhoid fever in hospitals varies from 7 to 20% and in private practice from 5 to 12%, and the usual figure for estimating the number of cases of typhoid, based upon the number of deaths, is 10%, it is evident that we have in Baltimore at the present time very complete returns for this disease.

The officials of the Board of Health, particularly Dr. Jones and Dr. Stokes, have been interested in this complicated and serious problem of typhoid fever for some time, and in the annual report issued by Dr. Bosley for the Health Department for 1907, Dr. Jones has considered the matter at great length and any observations that can be made upon the disease here must start with his paper as the basis.[1]

In discussing this question, Dr. Jones came to the conclusion that 10 possible sources of our typhoid might be named:

1. Bathing in polluted water.
2. Privy wells.
3. Flies.
4. Importation.
5. Contact.
6. Hydrants in yards.
7. Water wells.
8. Raw foods.
9. Milk.
10. Drinking water.

When we now come to a consideration of these possible sources we are confronted with apparently a hopeless task. The factors which enter into the situation are so diversified, our information concerning the disease in general is so defective in those very points which are of prime importance in elucidating the problem, especially the conditions which govern the life history of the responsible parasite outside the human body, that with the evidence at hand it almost seems as though any deductions which we can make must be based upon insufficient grounds. Investigations of typhoid fever in other cities where the conditions are not unlike those in Baltimore, especially in Washington and in Richmond, while fruitful scientifically and slowly solving the problem for those communities, nevertheless do not give us conclusions which can be applied without great caution to our own city. The problem is essentially one which must be worked out by each center of population for itself.

Our typhoid fever may be said to present three definite aspects. First, it has existed in Baltimore from the earliest times, fluctuating somewhat from year to year, never falling below a certain level, but occasionally rising above this level to a point, as in the year 1910, where it may be regarded as epidemic. Secondly, the disease arises essentially as a result of local conditions. There is little or no evidence that our typhoid fever is imported from other districts. We have in our midst the very influences which lead to its continuous propagation. Thirdly, with the exception of the year 1906, when several small epidemics occurred during the colder months and were clearly due to polluted milk supplies, the cases occurring exclusively among the patrons of certain dairies, we have little winter typhoid compared with our *marked summer rise*. Chart I for the year 1910, prepared from the Board of Health Reports, shows this very clearly. But it must be remembered that the variation here represented is not characteristic of any particular year, but represents a distribution of the disease by months which is peculiar for our typhoid. While we usually have but few cases of the disease in the winter months, it never disappears entirely. *Typhoid fever with us is a winter as well as a summer disease.* With the onset of warm weather, however, the case incidence and the number of deaths show a very rapid increase. During July the figures for both run up rapidly; during August they increase still more and the maximum is reached usually in September or in October. With the beginning of cold weather in the autumn the number of cases begins to diminish; this diminution becomes marked in November and December, but at no time do the cases entirely disappear. During the months of January, February, and March the disease remains quiescent only to break out again during the next warm season with the most dreadful certainty. A repetition of the summer epidemic each year can be predicted with absolute confidence.

We have thus two constants, the *continued presence* of the disease in Baltimore, and the *marked seasonal variation*. Dr. Jones, in considering the ten possible sources of typhoid fever which we have previously mentioned, has been able to eliminate such factors as bathing in polluted waters, well water, hydrants in yards, privy vaults and importation, from responsibility as epidemiological factors. Five possible sources of typhoid remain for us to consider.

1. *Raw foods.*—A number of articles of diet which are eaten raw, such as shellfish, vegetables and fruits, are popularly supposed to be intimately associated with enteric fever, and there can be no doubt that the typhoid bacillus may be carried by uncooked foods in certain special instances. Typhoid due to oysters polluted with sewage has been reported by Conn[2] and recently Buchan[3] has called attention to the serious contamination of the shellfish sold in Birmingham, England, and has indicated their importance as a possible source of the disease. As far as oysters are concerned in Baltimore, they may probably be eliminated from responsibility. Our typhoid is at its lowest ebb at the very time when oysters are consumed in the greatest quantity and has its especial prevalence in the months when the sale of the bivalve is forbidden by law. While raw fruits and uncooked vegetables may play a part in the spread of the disease, no satisfactory proof of this has thus far been presented.

2. *Contact.*—Our knowledge of the "chronic bacillus carrier" and the disastrous results which follow his entrance into a family or into a community has served to again emphasize the importance of contact infection in enteric fever. The many investigations in Germany, England, and in this country, especially in New York and Washington, indicate how many of our typhoid patients have previously come into close association with cases of the same disease, especially in its milder forms. They also serve to show that many attacks

which on first consideration cannot be explained on the basis of contact, on careful study and search are apparently clearly the result of a more or less intimate connection with previous cases. In this city we may probably have underestimated the proportion of cases of this character, and Baetjer [4] has recently called attention to the important rôle which contact may play in our country typhoid, reporting 17 cases in two houses. During the past summer direct infection may have had a very significant part in spreading the disease, especially in the poorer sections of the city. The newspapers frequently stated that several cases had been found in one house or in one family. In a certain instance an extraordinarily large number was reported from a block of houses on East Chase street, and here the infectious material seems to have been transmitted directly from person to person. In general, however, the records of the Health Department indicate that in the majority of instances the cases of the disease occur singly in houses, but a small number of two-case and three-case houses having been discovered. Furthermore, we have typhoid summer and winter alike and the factor of contact infection will not explain the great increase of the disease in the summer months—that is, the marked *seasonal variation* or *summer rise*.

3. *Flies.*—One of the most attractive and plausible theories to explain a great prevalence of enteric fever in any community during the hot days of summer is to attribute the spread of infection from individual to individual to the agency of flies. The work of Levy and Freeman [5] in Richmond, where a campaign directed against the fly seemed to be effective in limiting the cases of typhoid in that city, has been quoted far and wide and the conclusions reached by these authors frequently applied to such cities as Washington and Baltimore, where the climatic conditions and character of the population are almost identical with those of Richmond. The importance of the house-fly as the carrier of infection has also been emphasized by Jackson [6] in New York, in seeking an explanation for the cases which appear in that metropolis. Still it must be remembered that in this city we suffer from typhoid not only during the fly season but during many months of the year when responsibility cannot be fastened upon these pests. During the year 1910 we had 26 deaths from typhoid fever and 106 new cases reported to the Board of Health for the month of December. While flies may be carriers of infection during the season when they are especially abundant and may thus explain the increase of the disease during July, August and September, they can play but a subsidiary rôle in the cases which occur during the winter, the early spring, and the late fall. Furthermore a great deal more knowledge as to the life-habits of these insects and the occurrence and distribution of the various species in Baltimore must be obtained before we can justly conclude that their activities are important epidemiological factors in this community.

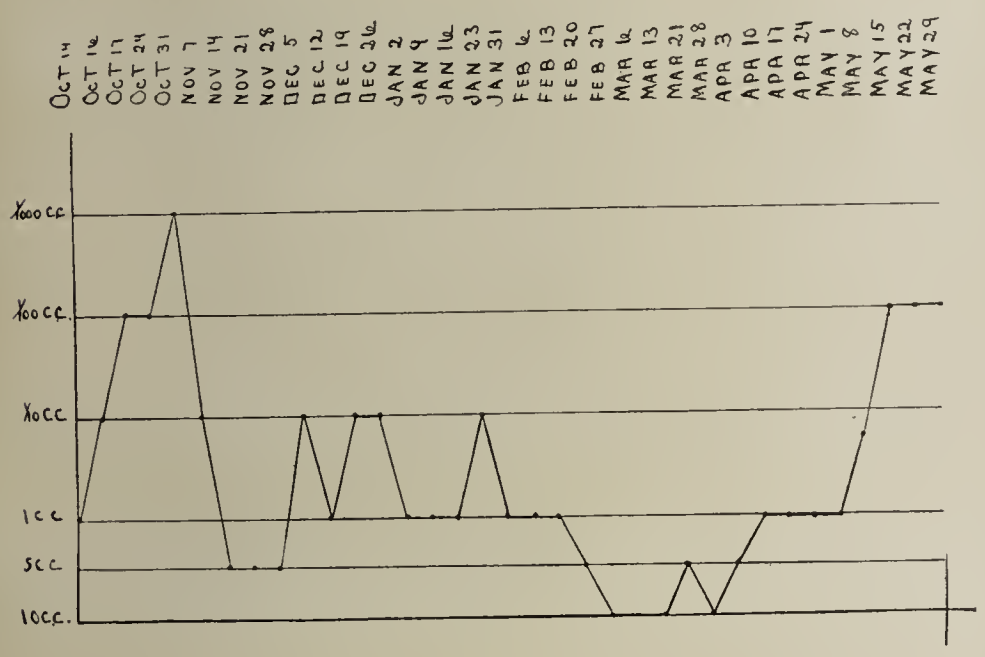
4. *Milk.*—The milk supply of Baltimore comes from a wide district of farming land in the more or less immediate vicinity of the city. It is handled by a number of dairy companies which either produce it on their own premises or collect it from small farmers, and then ship it in bottles or in large cans holding a number of gallons, to the principal railroad stations. During transit no attempts at refrigeration are made. From the stations in the city it is distributed in wagons from house to house or sold directly to the consumer in the little shops dispersed through the poorer sections of the community. Considerable time necessarily elapses between the hour of milking and the ultimate consumption of the product. The various dairies often handle milk from a number of different sources, this milk being mixed in bulk and again parceled out in small quantities. As a result the individual samples sold over the counter may sometimes represent milk collected from widely scattered areas. The inspection of milk in the city limits is wisely carried out by the officials of the Health Department and is as effective as the present laws permit. Still a proper and thorough regulation of the traffic at the proper point, that is, on the premises of the farmers who make a business of producing the milk, is not possible. The larger and more prosperous milk dealers have adopted the modern sanitary regulations which ensure cleanliness and are making conscientious efforts to furnish our citizens with a product which will meet the present-day demand for milk of a proper chemical composition and a low bacterial count. In many of the small shops, however, where milk is sold by the quart, pint, or even half-pint, the filthiest conditions prevail. Refrigeration is either not regarded as necessary or the measures which are carried out are of little value in maintaining the milk at a low temperature. The milk cans are frequently opened as the milk is doled out to the consumers one after another, and since the rooms where the milk is sold are often the living rooms of a large family, it is thus exposed to contamination of various descriptions.

For a number of years now we have been making frequent examinations of the milk found in the poorer quarters of the city in the vicinity of the Johns Hopkins Hospital. While these examinations have not been made through the entire year, nor with sufficient frequency to furnish positive conclusions, they indicate clearly that much of the milk sold to the poor people is badly polluted. The bacterial count frequently runs up into the millions and is uniformly above even the most liberal standards of purity. Recently one of our advanced students, Mrs. de Angulo, has been making weekly examinations of samples of milk collected in East Baltimore. In some instances she has found 50,000,000 bacteria to the cubic centimeter. In a number of cases the count varied from 10,000,000 to 25,000,000, and in nearly every sample obtained at the small shops where the milk is sold from milk cans the count has been 3,000,000 or over. If such a degree of pollution is found during the winter months, what must be the amount of bacterial life in this product in the hot summer weather? Such extremely dangerous conditions are found, of course, only in certain regions and in the small shops. The bottled milk furnished by the better dairies shows usually a low bacterial count, and indeed certain companies furnish milk which would

pass the most rigid qualifications that could be reasonably imposed.

5. *Water.*—The far-reaching importance which must be attached to the Baltimore City Water Supply as a source of our typhoid fever has previously been indicated. Our water is derived from two main streams, the Gunpowder River and Jones Falls. For many years we have made a study of the Gunpowder water and have demonstrated with great regularity a serious and constant pollution in it.[7] *Bacillus coli* can always be obtained in the majority of 1 cc. samples examined. It is frequently present in a dilution of 1/10 and rarely in higher dilutions, 1/100. Together with this organism there are many other bacteria of intestinal origin. *Bacillus alkaligenes,* which so closely resembles the typhoid bacillus, is often found on the plates and certain liquefying bacteria such as *Bacillus cloacae,* which may be regarded as characteristic of sewage, are occasionally encountered. The bacterial count varies greatly, apparently bearing some ratio to the rainfall and amount of water in the reservoirs. It is usually somewhat under a thousand to the cubic centimeter, but may exceed this number,

Chart V.—Pollution of Gunpowder water. Fermenting organisms. October, 1910, to June, 1911.

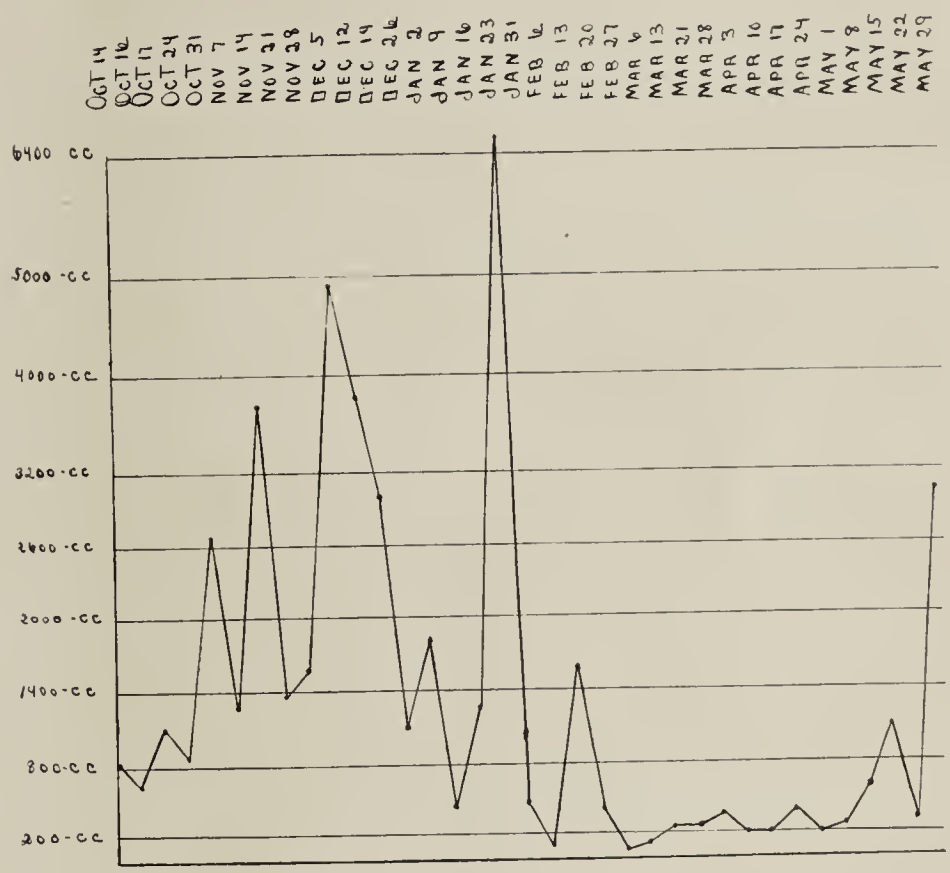


running up to between ten and fifteen thousand. The examination of the water taken from the spigot thus shows a pollution which is of a decidedly serious character and practically permanent. The findings at the tap are amply explained by the conditions which prevail along the watershed of the Gunpowder River. The sewage from numerous farm houses and small settlements of working people passes directly into this stream or into its tributaries, certain of which, notably Western Run, Beaver Dam Run and the Oregon Branch, are grossly polluted.

Dr. Stokes at the Board of Health has obtained much the same results as ours in regard to the Gunpowder water. In addition he has made a special study of Jones Falls and Lake Roland, and he and Hachtel have even succeeded in isolating the typhoid bacillus from Towson Run, one of the small streams which passes into the latter body of water.[8]

Beginning in October, 1910, when typhoid fever was raging in the city of Baltimore, we have made regular tests of the Gunpowder water, estimating the extent of pollution by using the fermentation tube and by counting the number of colonies. The bacteria present at various periods have been isolated and submitted to careful study and identification, largely in the hope that we might determine the value which should be assigned to the presence of various liquefiers. As can be seen from Charts V and VI, the pollution of the water in October had reached a most dangerous grade. *Bacillus coli* or some other fermenting species was constantly present in a dilution of 1/100 and on one occasion in a dilution of 1/1000. The number of microorganisms was also much above that usually accepted as the standard of purity. At this time Maryland had been suffering from a prolonged drought, and the water in

Chart VI.—Pollution of Gunpowder water. Bacterial count. October, 1910, to June, 1911.



Loch Raven and in the Gunpowder was at the lowest ebb it had reached for years. The filth which is regularly present in the stream had evidently been greatly concentrated and the appearance of several thousand colonies to the cubic centimeter and especially the extraordinary degree to which the water could be diluted without causing the disappearance of the intestinal bacteria indicate how totally unfit for use the Gunpowder water was at this time. The pollution of this stream, which was then the main supply of the city, Lake Roland having been temporarily eliminated, continued excessive during the autumn months and early winter. Not indeed till February of this year did conditions improve, the bacterial count come down to normal and the intestinal microorganisms disappear from the fermentation tubes. Recently, however, evidences of sewage contamination are again shown by our studies and during the month of May, 1911, the Gunpowder water reassumed the filthy character it presented last October.

Discussion.

It may thus be seen that with the evidence at hand but an unimportant rôle can be assigned to raw foods, to contact infection, and to flies as epidemiological factors in our typhoid fever. While a certain proportion of our cases may be due to contact and while the number of cases may be augmented through the agency of flies in the fly season, the activity of these insects cannot be made to explain our winter typhoid, nor can the agency of contact explain our great summer rise. A combination of the two factors might be suggested to explain summer and winter typhoid alike, but the problem is not so simple and two other possible sources of infection must be considered. These other possible sources are *milk* and *water*. The milk supplied to the people of Baltimore, especially to the poorer classes, is frequently loaded with microorganisms and would not meet any reasonable requirements based upon a bacteriological examination. The regulations adopted by other cities if applied to Baltimore would probably stop the sale of much of the milk now offered in certain of the crowded districts of the city. This milk pollution is amply explained by the conditions on dairy farms, along the route of travel, and in the shops where the milk is sold. In the long and tortuous journey which the milk drunk in Baltimore must travel from the udder of the cow to the mouth of the consumer, this valuable and almost indispensable article of diet is exposed to frequent chances of contamination with dust, dirt and filth. The abortive attempts at refrigeration are manifestly insufficient to prevent the growth and multiplication of those microorganisms which find accidental entrance. If milk can serve as a source of typhoid fever, we have in the city of Baltimore at the present time ideal conditions for the spread of this disease. Furthermore, the very months of the year when the cases are at their maximum are those months when we can reasonably suppose that the life of the typhoid bacillus in milk will be considerably prolonged, namely, in the hot summer season. Moreover, several outbreaks of the disease in the winter months have been definitely traced to certain dairies, as in the year 1906. Whether the uniform distribution of the cases of typhoid over the entire city which is characteristic of Baltimore can be brought into harmony with milk-borne infection is not quite clear. It must be said, however, that the typhoid of Washington seems to bear a direct relation to the city milk supply, and yet the distribution of the disease in that city is fairly uniform and is similar to the distribution which has been noted here. Thus the utmost stress must be laid upon milk in considering the epidemiology of our typhoid and next to our water supply milk must be regarded as the factor of the greatest importance.

The serious and dangerous pollution of our city water, which has been emphasized by Dr. Stokes and by ourselves, may well be pointed to whenever the subject of typhoid fever is under discussion. That the contamination has been increasing markedly during the past two or three years is evident from the results of the many examinations which have been made. Recent experience in both Richmond and Washington, however, indicates how dangerous it may be to attribute enteric fever to water supplies, even though the filtration of water in other cities or the change from a polluted to a pure supply has been followed by a marked reduction of the typhoid. Still one point of great importance has been brought out by the investigations of the past year. The extent of pollution of the Gunpowder water, or the concentration of the sewage present in it, shows the same variation as does our typhoid fever. Thus typhoid was as its height in September, October and November of last year, and at this time the water used in Baltimore was showing its maximum pollution. By December the number of cases had come down markedly but not to anything like our normal for this month. At the same time, the pollution of the water had diminished in quantity. During the past winter months the typhoid almost disappeared from our midst, and for this period the water showed comparatively little sewage. With the onset of hot weather the pollution of the water supply has again become excessive and the returns to the Department of Health indicate that our typhoid is also becoming prevalent.

Whether this close correspondence or parallelism between the amount of this disease in our city and the extent to which our water supply is polluted is anything more than a coincidence cannot be decided with the evidence at hand. Mere parallelism is no proof of etiological relationship, and until we are able to eliminate water as a factor in the existence of typhoid in Baltimore by the adoption of filtration plants or by its sterilization or disinfection we will not be in a position to explain the disease satisfactorily. For the present the question has only a theoretical interest. Our constantly and persistently polluted water must be regarded for the present as the main source of our typhoid fever. It is absolutely essential for the health of the citizens of Baltimore that the most stringent regulations be enforced in controlling our water supply, and that every effort be made to hasten the construction of the sand filters now being prepared for the Gunpowder water. Until these filters can be utilized the water should be sterilized by the addition of some chemical disinfectant, preferably by the hypochlorite or bleaching powder method.

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THE RECENT EPIDEMIC OF DIPHTHERIA IN THE JOHNS HOPKINS HOSPITAL AND MEDICAL SCHOOL: GENERAL PROCEDURES ADOPTED.*

By William W. Ford, M. D., D. P. H.,

Associate Professor of Hygiene and Bacteriology, The Johns Hopkins University.

During the last week in January and the first two weeks of February of this year (1911) a number of cases of diphtheria occurred in the Johns Hopkins Hospital and Medical School. On January 25, a pupil nurse with the disease was admitted to the Isolation Ward, and on February 3 a patient in the men's ward, Ward F, developed clinical symptoms of diphtheria, and a throat culture showed the Klebs-Loeffler bacillus. He was immediately isolated and no further cases appeared at that time in the ward from which he was taken. On February 9, a pupil nurse in charge of the children in Ward G, the women and children's ward, developed diphtheria and on the following day an employee in the baggage room was found with an infected throat. These cases all presented the clinical picture of a mild type of the disease and rapidly recovered. On February 11, a child in Ward G, an old burn and skin-grafting case, exhibited a bloody nasal discharge. It had been fretful and ailing for some time and the attention of both doctors and nurses had been directed to its condition. When the discharge appeared it was at once examined and the diagnosis of nasal diphtheria established. This infection proved to be virulent in character, the child dying, despite the vigorous use of antitoxin. It had evidently had the disease several days before clinical symptoms were noted. No idea that the contagion would spread was then entertained, but on February 13 two more cases developed in children in the same ward, Ward G, and two days later a fourth-year student on duty as a clinical clerk in this ward was found infected with the characteristic organism. In a period of twenty-two days eight cases of the disease had thus made their appearance, five of them located in Ward G, three in children patients and two in individuals rendering assistance in the care of these patients.

This number of cases of diphtheria was by no means out of the ordinary, either for large general hospitals of the size of the Johns Hopkins or for this Hospital itself. We have always had an occasional Klebs-Loeffler infection and shall always expect such sporadic cases. We live in a community where diphtheria is ever present, and the extension of the outside infection to the Hospital is never unexpected, nor is it usually a matter of concern. But when the Clinical Clerk on Ward G was found with the disease, and it was realized that three other cases had developed in the children on the same ward, it was suspected that the infection might have spread and a more or less systematic examination of patients, nurses and students in this ward was carried out. No cases were then brought to light, but four days later another fourth-year student in Ward G was found infected. This was on February 20, and on the following day diphtheria was discovered in three adult patients in Ward G, in three nurses in this ward, in another nurse, a room-mate of one of the infected Ward G nurses, and in a nurse in the general operating room, who had handled Ward G patients.

This more or less sudden outbreak of diphtheria in Ward G, or rather this sudden spread of the contagion, was viewed with great uneasiness by the medical internes and especially by the Resident Physician, Dr. Sladen, and by Dr. Austrian, who had been examining the cultures. The occurrence on one day of eight cases of diphtheria associated with one ward indicated a firmly seated focus of infection and a by no means remote possibility that this infection would spread in a number of directions. The very free access to the wards which our students enjoy added to the body of patients, doctors, nurses and attendants who might become infected, another fairly large and somewhat widely distributed group of individuals who could carry infection to various points. Actuated by a well justified concern, on February 21, after these eight cases of diphtheria were discovered, the Resident Medical Staff instituted a systematic examination of the hospital population. The throats of all were carefully studied for local signs of infection, and on the slightest appearance of suspicious symptoms the individuals were segregated and cultures taken. The following day three more cases of diphtheria were brought to light, an adult patient, a nurse in Ward G and a medical interne in another ward. On Thursday, February 23, seven cases were discovered, two more children in Ward G, three nurses and a member of the second-year medical class. On Friday, February 24, eleven cases of diphtheria made their appearance, two more nurses, a patient in Ward F and eight medical students.

At this time the situation was regarded as extremely serious by all the men who were working on the wards. Cases of the disease were cropping out with great rapidity and in a number of different areas. It was evident that diphtheria had gotten a firm foothold in the institution. From January 25 to February 25 thirty-eight cases had developed. This was despite the fact that the cases were recognized early, the diagnosis established soon after the appearance of clinical symptoms, complete isolation of all the patients carried out and energetic cleaning and disinfection employed to rid the infected localities of the contagious material. In brief, all the measures which under ordinary circumstances are employed to prevent the spread of the Klebs-Loeffler bacillus had been adopted and yet the disease was steadily increasing in intensity. The occurrence on two days of eighteen cases of diphtheria was too serious a matter for both the Hospital and the

* Paper read at the 1911 meeting of the Interurban Clinical Society.

Medical School not to be regarded with considerable uneasiness. It was furthermore clear that the disease was spreading in two directions, independently and simultaneously: first, in the group of persons associated with Ward G, patients, nurses and assistants, and individuals in the Nurses' Home, who had been in contact with the Ward G nurses; and, secondly, in the student-body of the Medical School. In regard to the first group of people two possibilities existed, one that a focus of diphtheria existed in Ward G, from which source it spread to the Nurses' Home, the other that a focus existed in the Nurses' Home, from which point it spread to the patients in the ward. In the second group, the medical students, cases had been discovered in all the classes and the appearance of a greater number in the first- and second-year students, who do not come into the hospital, than in members of the third- and fourth-year classes, who might be infected from ward cases, was a proof of the independent transmission of the disease among the students themselves. Various avenues by means of which the infection might be spreading in the student-body were suggested, the most probable channels being the Lunch Room in the basement of the Physiological Building, where about a hundred men and women from all four classes take their midday meal, and the various students' clubs and boarding houses.

At the meeting of the Advisory Board of the Medical Faculty on Friday, February 24, the many details of the situation were presented by Dr. Barker, and it was decided to close the Medical School. A committee was appointed to take charge of the situation. This committee, known afterwards as the Diphtheria Committee, consisted of Dr. Williams, Dr. Barker and Dr. Ford. Dr. Norton was asked to become an ex-officio member as the Acting Superintendent of the Hospital. It should be mentioned that only by the active and willing co-operation of Dr. Norton with this committee was it possible to carry out the various measures which were suggested to stamp out the disease. To the Diphtheria Committee all questions relative to the epidemic in both Hospital and Medical School were referred.

On Saturday morning, February 25, Dr. Williams, the Dean of the Medical School, posted notices stating that the institution was closed temporarily. Later notices were sent to all the students urging them to remain in Baltimore, to keep in close touch with the school authorities and to avoid appearance in public places like theaters and churches. On the same morning the Diphtheria Committee held its first meeting. The various features of the epidemic were discussed at length and certain general measures were decided upon. These measures included the further examination of all the Hospital inmates, patients, doctors, nurses, orderlies, etc., the taking of routine throat cultures from all the medical students, and the cleaning and disinfection of the medical buildings. An investigation into the conditions of the many boarding houses where the students live, to bring to light any hidden foci of infection, was also considered advisable, and Dr. W. L. Moss was asked to undertake this latter work.

At this time it was deemed of great importance to get in close touch with the Department of Health of the City of Baltimore, and Dr. Moss and Dr. Ford, at the request of the committee, had a long conference with Dr. Jones, Assistant Commissioner of Health. At this conference a number of plans of work were considered. Dr. Jones suggested at once the importance of taking throat cultures from all the inmates of the students' boarding houses to determine whether the infection was spreading or likely to spread to the city. He put the resources of the Health Department at the service of Dr. Moss in his investigation and made him a temporary official of the Department. Dr. Jones expressed his great desire to co-operate with the Diphtheria Committee in any way possible, and all questions affecting the relationship of the Hospital and the city, such as the discharge of patients, were thereafter submitted to him for decision.

On Saturday, February 26, six additional cases of diphtheria developed and on the following Sunday eight more, three in members of the Faculty or their families. When the committee met on Monday fourteen cases had thus been added to the thirty-eight already reported, making a total of fifty-two. It was evident that the disease was spreading rapidly and it was therefore decided to close the Dispensary, partly in order to give it a thorough overhauling, and to admit no more patients to the Hospital except certain urgent cases who were to be warned of the danger.

By this time the various measures of cleaning and disinfection, of taking routine cultures from the throats of the Hospital and Medical School population, the complete isolation of individuals with positive throat cultures, the detention of suspects, had been put in operation. It was apparent that some of the patients were rapidly recovering and would soon be ready for discharge. A number of non-infected patients were also anxious to leave the Hospital. Dr. Jones was therefore appealed to, for a ruling in regard to the matter. He decided that the patients should be divided into three groups and treated as follows: First, all persons who had recovered from diphtheria could be discharged when two negative cultures from nose and throat separated by a forty-eight hour interval had been obtained. Secondly, all persons exposed to diphtheria and not contracting the disease could be discharged when one negative nose and throat culture had been obtained. Thirdly, all persons not exposed to the disease could leave when one negative throat culture had been secured. Acting upon these rulings on Tuesday, February 28, Dr. Norton posted notices in the Hospital and began the discharge of patients.

The cleaning and disinfection of the Medical Building was put in charge of the writer and presented a special problem which may be considered briefly. The buildings are large, divided into many rooms, devoted to all sorts of purposes, and were in active use at the time of closure. The presence of large corridors and stairways, establishing a free communication often between basement and attic seemed to render any gaseous fumigation valueless. Largely upon the advice of Dr.

Jones, it was decided to disinfect with formaldehyde wherever possible, but to rely mainly upon a thorough cleansing of the floors and walls to a height of about six feet, after the buildings had been allowed to rest absolutely undisturbed for 24 to 48 hours to allow the dust to settle. Attempts which were made to disinfect some of the rooms with formaldehyde gas obtained from such preparations as briquets of formanganate and patent candles which on burning evolve this vapor, demonstrated the uselessness of the procedure. In a few minutes after the evolution of the gas had been brought about the odor of it had disappeared from the rooms, the many openings about the doors and windows, the heating apparatus, and the ventilating shafts, permitting it to pass into other parts of the building. It was evident that some method of obtaining a continuous evolution of the gas lasting a number of hours must be hit upon if an effective disinfection of these large buildings was to be obtained. At the suggestion of Mr. Hartley, head janitor of the Anatomical Laboratory, this object was accomplished by the long-continued boiling of solutions of 40% formalin in water in the proportion of about one part to three. The windows and doors of the buildings were tightly closed, all the inside doors leading from the rooms to the corridors opened and saucepans containing the formalin mixture were boiled over Bunsen burners in a number of different localities. A constant evolution of the gas lasting six to eight hours was thus obtained, the atmosphere of the building being saturated with the vapor for a considerable period of time. The flames of the Bunsen burners were extinguished by turning off the main supply of gas in the basement and on the following day the buildings were opened, thoroughly aired and the work of cleaning undertaken. The floors and walls were first washed with soap and water and then wiped off with some disinfectant solution, either a solution of carbolic acid or one of corrosive sublimate. Whenever the latter substance was used it was followed by another washing with soap and water.

In buildings where the presence of animals or expensive apparatus likely to be injured by the vapor of formaldehyde prevented this disinfection of the structure as a whole, the separate rooms were sealed up and fumigated by the Parke Davis formanganate briquets or by the Du Prey candles. These rooms were kept tightly closed for 24 hours and then the floors and walls were washed with soap and water and with disinfectants.

No bacteriological tests were made to determine the efficiency of the fumigation. The necessity for rapid work precluded any satisfactory observations, and it was realized that no method of disinfection is perfect. It was decided to carry out as vigorously as possible those methods which are recognized to be of the greatest value and to trust to a wise providence that the contagion would be destroyed. Afterwards, when more time was available, with Dr. Norton's help, a number of observations were made during the disinfection of Ward G. It was found that surface cultures of organisms like *Bacillus typhosus, Bacillus coli, Streptococcus pyogenes, and Bacillus prodigiosus* were killed when exposed to the gas generated by the Parke Davis briquets of formanganate. The organisms in the depths of the tubes remained viable however.

Special emphasis was placed upon the disinfection and cleaning of the Lunch Room in the basement of the Physiological Laboratory. From the beginning of the epidemic it was believed that it might be one of the main foci of infection among the students. Primarily it was the only place where there was a general meeting of the members of all classes. Again, certain practices in vogue there, such as cleaning the table-tops with napkins left by students who had already taken their lunch and departed, seemed to offer an abundant opportunity for the spread of any contagious material coming from the throat. This room was therefore fumigated and washed thoroughly on two occasions separated by an interval of several days, and when finally reopened certain changes were instituted in the care of the dishes and napkins.

The students were encouraged to disinfect their own rooms, and in many instances were supplied with material from a quantity of disinfectant which had been sent to the school from the Department of Health. In all the students' clubhouses and in the majority of students' boarding houses this procedure was carried out most energetically.

Certain special difficulties were met with in the work of cleaning. In the first place it was extremely hard to get labor because of the widespread fear of diphtheria which had been engendered in the minds of the various residents in the vicinity of the Hospital, partly because of the wide publicity which had been given the epidemic by the newspaper reports. In the second place it was believed that all the people working in the buildings would be exposed to infection with the Klebs-Loeffler bacillus and the problem of their proper care had to be met. Eventually, a sufficient number of active people were obtained to do the necessary work. No cultures were taken from the throats of these individuals during their time of employment. It was perfectly evident that if suspicion should arise that they stood in danger of infection under no circumstances could they be induced to remain at work. At the same time it was realized that these individuals should be carefully examined at the end of the period of cleaning and disinfection to determine whether any of them had become infected with the diphtheria bacillus. This work in the medical buildings was completed in about a week from the time it was started. On Saturday, March 4, cultures were taken from all the workpeople, the extra employees were discharged, and the control of the buildings turned over to the Dean of the school. One positive throat culture was found in a woman who had been working in the Physiological Laboratory. It was not absolutely certain that this woman became infected in this building, since we had no negative throat culture at the time she began her work there, but the presumption was in favor of this source of her contagion. This case proved to be of considerable interest and importance. The woman harbored diphtheria bacilli in her throat for a period of fully 20 days, during which time she had no clinical symptoms or signs whatever. All sorts of measures were carried out to rid her throat of the organisms, such as spraying with various disinfectants and

with antitoxin itself. She received as well the regular antitoxin treatment administered subcutaneously. Eventually two negative cultures from her throat were obtained by the officials of the Health Department, and she was discharged from quarantine. This was one of the few definite cases in this epidemic where the diphtheria bacillus remained for some time in the throat of an individual without causing the appearance of clinical symptoms.

The most perplexing question which the Diphtheria Committee had to decide was in regard to the use of prophylactic or immunizing doses of diphtheria antitoxin. This measure was discussed on a number of occasions. A large number, if not all, of the doctors and nurses in contact with the disease took this treatment soon after the epidemic broke out. It was a matter of great importance, however, to determine whether this procedure should be insisted upon with all the inmates of the Nurses' Home and with the members of the Resident Staff of the Hospital. The Health Department from the first had recommended prophylactic antitoxin as the only remedy which could be relied upon to stop the spread of diphtheria among the nurses. At the same time the administration of antitoxin is certainly followed in a few individuals by the appearance of disagreeable or untoward consequences and authorities are by no means agreed as to its value in checking epidemics. Relying upon several experiences in Baltimore where diphtheria has been stamped out of a number of institutions only when prophylactic antitoxin has been administered to all the inmates, upon reports from various hospitals for the care of contagious diseases in which this treatment is carried out as a routine measure with the children when diphtheria appears, and upon a number of publications as to the percentage of bad results which follow the use of antitoxin, the committee decided to recommend but not to insist upon this measure. Whenever antitoxin had been administered previously, wherever an authentic history of attacks of asthma could be elicited, contra-indications were recognized to the use of the remedy.

A careful record of the administrations of antitoxin was kept by Dr. Sladen and his staff. Over three hundred prophylactic doses were given, two hundred nurses receiving the treatment, forty-three students, and a small proportion of the resident staff. About seventy patients took curative doses of the remedy. Nearly all the individuals who received the antitoxin either for prophylactic purposes or to combat an existing infection with the Klebs-Loeffler bacillus developed some local signs. In most cases the reaction was limited to slight urticaria. In a few instances a pronounced œdema was noted with local tenderness and elevation of temperature in the dependent parts near the site of injection. In five cases characteristic serum disease appeared. In one of these cases, a fourth-year student, immediately following the injection of the antitoxin a typical anaphylactic shock developed with great dyspnœa, shivering, vomiting, and attacks of faintness with tendency to syncope. These symptoms lasted for a number of hours but eventually entirely disappeared. This student had received antitoxin previously and gave a history of asthmatic attacks in his youth. In the other four cases in but one or two instances had antitoxin been administered previously.

How far the prophylactic use of diphtheria antitoxin was instrumental in stopping this epidemic is not clear. A number of interesting facts were noted which indicate that its use did have a definite effect upon the spread of the disease. The only nurse in Ward G who refused antitoxin later developed diphtheria. Among the other nurses on this ward who received the treatment no cases of infection appeared. Of the six children in Ward G, all exposed to infection, four received prophylactic antitoxin. Of these four, two later showed positive cultures of the diphtheria bacillus, but had no serious symptoms. The two other children on Ward G, in whom it was not considered advisable to administer the antitoxin because of recent surgical operations, developed diphtheria later and died. Coincidently with or immediately following the general administration of prophylactic doses of antitoxin to the nurses in the Nurses' Home, the infection disappeared in this group of individuals, and it did not disappear until this measure was carried out. While thus no proof can be brought to show that this procedure was operative in controlling the infection, the majority of the men who administered the antitoxin and followed the cases of diphtheria afterwards were convinced that it had no little influence in checking the epidemic. At the same time the prophylactic use of diphtheria antitoxin is probably the one measure adopted which might not be carried out so vigorously should we have epidemics of diphtheria to deal with in the future. While in our experience no serious results developed from the use of this remedy, there is a very general sentiment against it in both doctors and nurses, and this feeling is undoubtedly justified by the observations which have been published.

On Friday, March 3, it was apparent that the epidemic was dying out. From a case incidence of eight on the preceding Sunday, the number of cases had dropped irregularly during this week. Two cases in the nurses appeared on Monday, no cases were reported on Tuesday, three were found among the students on Wednesday, four cases developed on Thursday, one student, one nurse, one ward doctor and one orderly, and two came to light on Friday among the laundry employees. Altogether but eleven had developed in five days, and these had such a varied distribution as to indicate that they were but scattering cases at the end of a general epidemic. On Friday, therefore, Dr. Williams sent notices to the students and instructors that the school would open again to the first two years on Wednesday, March 8; to the last two years on the following day, at which time the dispensary was to be opened again to the public. Cultures were taken from all the students and instructors and only those with negative reports admitted to the school. The exercises began again on Wednesday and by the latter part of the week the routine of the Medical School had been re-established in all the classes. The infected wards of the Hospital were cleaned and fumigated, the patients who had recovered were discharged and new patients again were received for treatment.

A few cases of diphtheria did show themselves after Friday, March 3, at which time it was thought that the epidemic was over and the decision to reopen the school was reached. Thus on March 6 a child in the Maternity Ward was found with a positive nose culture, on March 7 a student developed a positive throat culture, on March 16 another student showed the infection, and on March 19 one of the physicians in the dispensary. On March 22 the room-mate of the last-named student developed an otitis media which proved to be due to the Klebs-Loeffler bacillus. Since that time no cases have appeared either in the student-body or among the individuals living in the institution. Altogether 66 cases of diphtheria were treated in the Johns Hopkins Hospital, to which should be added 6 cases in orderlies or members of their families who for various reasons could not be treated in the Hospital but who evidently contracted the disease there, a total of 72 cases. Four deaths occurred, three in children and one in an adult, none of them, however, being uncomplicated diphtheria cases.

We shall probably never know the source of this epidemic of diphtheria. Baltimore always has cases of the disease, and at times during the winter season these cases may occur with some frequency. From these foci of infection in the city the disease frequently extends into the Hospital, but at no time previously has there been evidence of any wide invasion of the Hospital population, nor has the fear been felt that such an invasion was likely to occur. In the three and a third years from September 1, 1907, to January 1, 1911, there have been but forty-four diphtheria patients in the Hospital. These cases occurred in individuals living in widely separated parts of the city, of various ages and occupations. Occasionally several cases have developed on or about the same time among the nurses or among the medical students. Thus in May, 1908, there were 5 cases of this description. The infection died out but during the next winter a few scattering cases appeared in the Hospital inmates. In the year 1909 there were about eighteen cases of diphtheria admitted to the Isolation Ward, of whom six were in the Hospital population and two among the medical students. In 1910 there were altogether eleven cases, of whom four were nurses or pupil nurses in the Hospital. These cases occurred at longer or shorter intervals, and while they may have developed one from another, they may equally well have been simply extensions of the disease from the city. At no time was there any difficulty in controlling these infections, and at no time was there any fear that the disease would spread in our midst. This sense of security was rudely shaken by our recent experience, and the possibility that an infection of mild form and almost self-limited may at times assume the character of a rapidly spreading contagious disease will always be entertained here in the future.

Finally, the question arises as to whether the very drastic measures adopted to stamp out this epidemic were necessary and whether the cessation of cases was directly due to the introduction of these procedures. Such questions from their very nature cannot be answered. We can only say that at the time the measures were put in operation, diphtheria was spreading with great rapidity in the Hospital and Medical School. All the men intimately associated with the work, especially the members of the resident medical staff, were appalled at the way the cases were coming to light and it was generally believed that unless drastic measures were employed a widespreading and serious epidemic of diphtheria might develop in the institution. With the inauguration of the various preventive methods which were considered advisable the disease disappeared from our population, and we cannot help but believe that this disappearance stands towards our activities in the relation of effect and cause and not in the relation of a sequence of events.

INFECTION OF THE URINARY TRACT BY THE BACILLUS LACTIS AEROGENES, WITH A CONSIDERATION OF THE MODE OF ENTRANCE OF BACTERIA INTO THE BLADDER.

By John Arthur Luetscher, M. D.,
Instructor in Medicine, The Johns Hopkins University.

Following the introduction of exact bacteriological methods by Koch, there appeared, in addition to descriptions of morphology and motility, more or less accurate descriptions of the cultural characteristics of the bacteria found in cystitis.

From 1887 until 1892 a series of observations were made by French authors who found, in cystitis in man, a bacillus as the most frequent cause of cystitis. This bacillus appeared under various names. Morelle [1] and Denys [2] identified it as the *B. lactis aerogenes;* while it was later definitely proven to be none other than the *B. coli communis* by Achard and Renault,[3] Reblaud,[4] Krogius,[5] and later observers. Were it not for the fact that these early observations are still classed under the *B. lactis aerogenes,*[6] I should hesitate to give a more extended historical review.

A careful study of the originals in the light of present-day knowledge should leave no doubt as to the exact identity of this particular bacillus.

In 1887 Clado [7] isolated the "bactérie septique de la vessie," stating that this bacillus had not been described by any one.

This bacillus had rounded ends, and was actively motile ("movements of translation" as distinguished from "movements of place"); it travelled rather rapidly, in some in-

stances across the field of the microscope, and did not stain by Gram's method. The colonies on plates had an irregular outline, and the agar slant had a thin, opalescent growth.

In 1888 Albarran and Halle[8] isolated the "bactérie pyogène" from 35 out of 50 pathological urines obtained aseptically from the bladder. This organism was found 15 times in pure culture, and 20 times associated with other organisms.

This bacillus was 4 to 6 μ long, with a diameter of 2 μ, had rounded ends, and was motile in young cultures, but did not stain by Gram's method. The colonies on plates had rounded borders, and looked like drops of wax. In the gelatine stick, the culture formed a white stem with a white hyaline layer on the surface. They concluded that their bacillus was the same as that described by Clado.

In 1889 Doyen[9] isolated from urine in cystitis 10 bacilli and 4 micrococci. Of the bacilli, 9 did not liquefy gelatine, nor had they any other characteristics to distinguish them from the "bactérie pyogène" of Halle and Albarran.

During the same year Rovsing[10] isolated the cocco-bacillus urea, from 3 of the 29 cases under observation. According to Schmidt and Aschoff[11] this bacillus was probably none other than the "bactérie pyogène" of Halle and Albarran.

In 1889 Morelle (loc. cit.) found a non-liquefying bacillus in 13 of 17 cases studied, of which 6 were in pure culture. This bacillus was small with rounded ends, sometimes ovoid, and very variable in length. Its size was always influenced by the media. The bacillus was possessed of "movements of translation." No spores were found. On agar the colonies were round, glassy, smooth, and if discrete, reached 4 mm. in size. When translucent, an exquisite design of concentric lines was often observed. He noted both the opaque and the translucent type, presenting a pleomorphism which would lead one to believe them to be different species. The growth on potatoes was white to yellow, and showed bubbles of gas. It coagulated milk in two days, with acid production. It fermented glucose, with formation of CO_2 and H.

He concluded that his bacillus was identical with (1) the "bactérie septique de la vessie" of Clado, (2) the "bactérie pyogène" of Albarran and Halle, (3) the cocco-bacillus urea of Rovsing, and probably with the 8 species described by Doyen.

After a careful comparison of the morphological and cultural properties, he concludes that his bacillus is none other than the *B. lactis aerogenes* of Escherich. In comparing it with the colon bacillus, he admitted that there was a great similarity, and that their pathogenic action was the same.

The differences cited were that the *B. lactis aerogenes* developed on gelatine into higher and more circumscribed colonies, with regular outlines; that they were white and more opaque, while the colon colonies were gray and translucent; also that the *B. lactis aerogenes* colonies were viscous, while those of the colon were more dry. He ends with the following sentence: "Still the similarity is great, and one may perhaps some day demonstrate that they are only two varieties of the same organism."

Achard and Renault (loc. cit.) were the first to call attention to the identity of the "bactérie pyogène" and the colon bacillus. They compared two strains obtained from Albarran and Halle, one strain obtained by Gilbert and Girode from the bowels of a new-born, and various strains obtained from cases of pyelonephritis. All had the same morphology, the same motility under similar conditions, and the same cultural characteristics. They also found the pathogenicity the same.

At the same time Reblaud (loc. cit.) reported his work of the previous year, from which he concluded that the "bactérie pyogène" is identical with the colon bacillus. Charrin[12] took the same view.

In 1892 Krogius (loc. cit.) examined 17 pathological urines from cases of cystitis, and in 12 found a small motile bacillus with rounded ends, and of very variable dimensions. The urine was acid, with a particularly fœtid odor. He compared this bacillus with the "bactérie pyogène" obtained from Albarran and Halle and found them identical. Injected into the bladder of rabbits, his bacillus produced the same symptoms of purulent cystitis as the "bactérie pyogène." He also found that by growing the opaque type in sterilized normal urine for several weeks, it was transformed into the transparent type.

Laruelle found that by growing the opaque form in milk it was changed into the transparent type. Krogius was able to confirm this result.

We have thus a bacillus termed variously the "bactérie septique de la vessie," "bactérie pyogène," cocco-bacillus urea, *B. lactis aerogenes, B. coli communis,* all possessing the same cultural characteristics and the same morphology, active motility, and causing cystitis in 71 per cent of the cases examined.

Two points should suffice to prove that these cultures could not have been the *B. lactis aerogenes:*

1. All were actively motile—"movements of translation."

2. They occurred in about 70 per cent of the cases of cystitis, which figures correspond closely to the percentage of cases of cystitis due to the colon bacillus as shown by all of the later investigators.

The differences in morphology and the cultural differences on gelatine are now known to be insufficient and too variable to differentiate them as separate species.

From this period on, one finds the colon bacillus as the causative agent of cystitis in 50 to 71 per cent of all cases of cystitis, while the *B. lactis aerogenes* has only rarely been found. A careful search of the available literature revealed only a few isolated reports.

In 1899 Warburg[13] reported a case of bacteriuria in a man 54 years old, who was admitted to the hospital for a slight bronchitis. On the fifth day after admission he had a chill, headache, and a rise in temperature to 39° C. The fever continued for three days, and on the second day the urine became cloudy. A catheterized specimen showed a small bacillus, often coccus-like, which was not motile. It did not stain by Gram's method. On gelatine the growth was nail-like; on potato whitish yellow; it coagulated milk in 12 hours; in sugar bouillon it produced gas; it produced no indol.

In 1894 Heyse[14] reported a case of pneumaturia in a patient who was 23 years old, and in her second month of pregnancy. She suffered from a "myelitis lumbalis ascendens," completely paralyzing the bladder and rectum, necessitating catheterization three to four times each day.

The urine was at first clear, acid, and free from albumen and sugar. On the fourth day after admission the urine became cloudy, containing pus and red cells. Four days later a tympanitic tumor reaching to the umbilicus was observed, and the urine finally became alkaline.

The following organisms were isolated: a coccus which liquefied gelatine, a non-liquefying coccus, and a non-liquefying bacillus. The last was identified as the *B. lactis aerogenes,* and held by him as the cause of the pneumaturia.

This bacillus had rounded ends, but was so often like coccus that doubts were entertained as to its purity until gelatine plates were made. The bacillus was not motile and did not stain by Gram's method. No spores were observed. The growth on potato was several millimeters thick, grayish white, viscous, moist, and shiny, showing numerous gas bubbles. The bouillon was uniformly cloudy, forming a sediment. Milk was coagulated in 24 hours. It fermented glucose and lactose. The gas consisted of 63 per cent CO_2, 27 per cent H, and 8 per cent "undetermined rest." These proportions of gas stamp it as a true *B. lactis aerogenes,* according to Burri and Düggeli.[15]

In 1901 Wildbolz[16] reported a case of pneumaturia in a man 52 years old who was suffering from a gonorrhœal stricture which had to be dilated. Three weeks later he noticed gas at the end of micturition. The urine was cloudy, acid, and had a disagreeable odor. A non-motile organism was isolated which did not stain by Gram's method. It coagulated milk rapidly, actively fermented grape sugar, but did not form indol.

In 1894 Schnitzler[17] reported a case of pneumaturia in a nullipara 46 years old. In the fall of 1893 she noticed the passing of gas at the end of micturition, but did not suffer from any other symptoms. On December 11, 1893, a cystitis developed and the patient was catheterized by a midwife, from which time on she had to be catheterized several times a day. A short, plump, non-motile bacillus was isolated from the urine. This bacillus did not stain by Gram's method. The growth on gelatine was profuse. It formed gas even on sugar-free media. No note is made as to growth on milk or potato, the fermentation of glucose and milk sugar, the formation of indol, or the presence of a capsule. His conclusion was that his organism belonged to the colon group. Adrian and Hamm think that in the light of present-day knowledge this bacillus really belonged to the lactis aerogenes group.

In 1896 Trumpp reported 29 cases of cystitis in children, one of which was due to the *B. lactis aerogenes.*

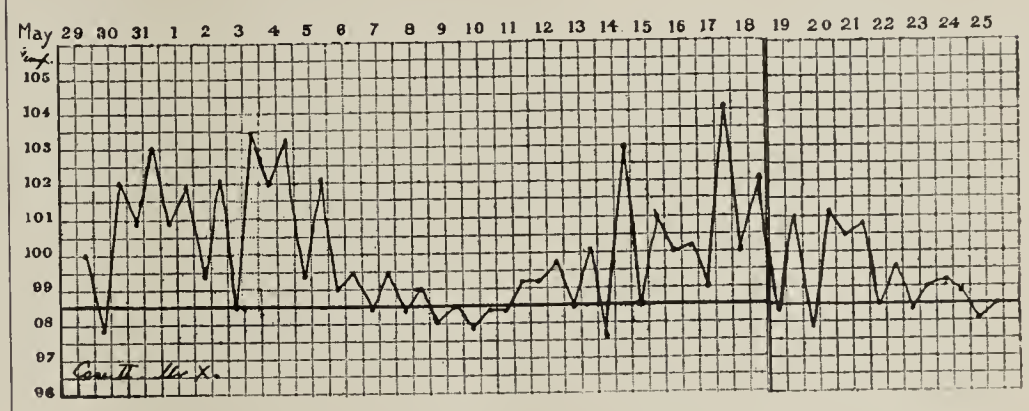
My personal observations were made on two cases with the following histories:

Case I.—Mrs. X, aged 28, during the second month of first pregnancy complained of frequent micturition which direction as to diet, fluids, and rest did not relieve. The symptoms became aggravated with marked tenesmus, bearing-down pain, and great frequency of micturition. Her condition was such as to require rest in bed with a diet of milk and water, also suppositories of opium to relieve the straining. She had no pain in the region of the kidneys, and her temperature was never over 99° F. The urine was light yellow, acid, and contained a sediment consisting chiefly of leucocytes with an occasional red cell. Albumen and sugar were absent.

Bacteriological Findings.—Each of two catheterized specimens taken ten days apart showed the *B. lactis aerogenes* in pure culture. The condition persisted for four weeks with a marked tendency to recurrence whenever the urotropin was omitted. Later cultures were negative.

Case II.—On May 25, four days after the acute symptoms in his wife had shown themselves, Mr. X, husband of Case I, developed a urethritis, accompanied with a yellowish, watery, acrid discharge which contained a few pus cells but no gonococci. He suffered from frequent micturition and a marked tenesmus requiring opium suppositories. The urethral discharge disappeared after the first day of rest in bed, on a diet of milk and water. The tenesmus and frequency of micturition also abated. The temperature, which was at first practically normal, after four days reached 103° F., as shown in the accompanying chart.

There was marked prostration, headache, and some nausea. These constitutional symptoms so overshadowed the local process



On June 9, fourteen days after onset, the temperature reached normal and remained so for two days, after which the patient began to complain of pain in the right abdominal region, extending into the inguinal ring on the following day. Twenty-four hours later a marked epididymitis had developed. The temperature reached 104° F., and the fever continued until June 26. The case terminated in a complete recovery with no recurrence.

that a blood culture was made on May 31, and a Widal test on June 3. In both, the results were negative. A physical examination revealed nothing. The prostate was not enlarged or tender. The urine was acid and cloudy, the last portions being especially turbid. At times a decidedly bloody tinge was noted. On microscopic examination, the sediment consisted entirely of leucocytes and red cells.

A bacteriological examination of the urine was made on the ninth and fourteenth day of the disease, and each time the *B. lactis aerogenes* was found in pure culture. The urine was obtained aseptically by means of a silk olive-tipped catheter, after previously irrigating the anterior urethra with a sterile boric acid solution.

Cultural Characteristics of Organisms Isolated.

In the hanging drop, Brownian motions were observed, but never independent movements such as to change the relative positions of the organisms. Cultures of different ages were tried, always with the same results.

Some difficulty was experienced in determining whether we

were dealing with a coccus or a bacillus. Even in stained specimens there was doubt as to whether the culture was pure, until plates were made.

The organism was a small bacillus, with rounded ends; coccus forms were frequent. It did not stain by Gram's method. Capsules were readily demonstrated.

On agar plates, the colonies reached the size of one millimeter in diameter in 18 hours, and had a bluish opalescent appearance by transmitted light. Under the microscope, the colonies usually had a regular outline, while in some the borders showed slight undulations. They were translucent, with opaque and granular centers. The deep colonies were wedge-shaped and opaque.

The agar slants showed a bluish opalescent growth by transmitted light, one millimeter wide after 24 hours, and with raised edges.

On potato there was a heavy, yellowish white, viscous growth, several millimeters thick, rapidly covering the entire surface. The older cultures showed a deeper yellow color. No gas bubbles were observed.

Milk was coagulated in 24 hours with acid production.

Glucose agar stick cultures were much split up by the accumulated gas. In the fermentation tubes, saccharose solutions showed considerable gas production.

The morphology, capsule formation, absence of motility, rapid coagulation of milk, together with the gas production, leave no doubt as to the identity of the organism. The rapid coagulation of milk excludes the Friedlander bacillus.[18]

Mode of Entrance of the Bacteria into the Bladder.

The bacteria may invade the urinary tract through the urethra, through the kidney, or from an adjacent abscess or other inflammatory process.

It is usually assumed that when there is no history of catheterization the infection must be an endogenous or descending one. There are two considerations which controvert this view:

1. The greater frequency of cystitis in women than in men, when there is no explanation of the mode of entrance of the bacteria into the bladder other than difference in sex.

2. The frequent existence of bacteriuria without infection of the ureters when no instruments have been introduced.

1. Relative frequency of cystitis in men and women in which there is no explanation of the mode of entrance of bacteria into the bladder other than difference in sex.

In general practice I have been impressed with the frequency with which one meets with cystitis in women, and the rarity of cystitis in men, if one excludes the cases due to gonorrhœa, tuberculosis, and diseases in which the bacteria are obtained by blood culture, such as typhoid, pneumonia, septicæmia, etc., and in those patients on whom instruments have been passed.

The gynecologist sees only women and the male genito-urinary specialist sees only men, so that neither has an opportunity to make a comparison. Nevertheless, the gynecologist must be impressed with the great number of cases of non-gonorrhœal cystitis in women who have never been catheterized; and the male genito-urinary specialist must be struck with the fact of the rarity of a non-gonorrhœal cystitis in the male who has never been catheterized, and who is free from any urethral or prostatic disease. A review of the histories of the large series of cases reported bears out this contention.

Of Rovsing's[19] 87 cases of bacteriuria and cystitis, 66 were male, and 21 female. Of the 66 male patients, definite mention of catheterization, fistula, or neighboring abscess was made in 51, or 88 per cent. Of the 15 remaining cases, one had phymosis; three had incontinence (one of which was due to tabes); five had retention due to stricture; and one an enlarged prostate. These therefore had a continuous column of urine through which the bacteria could readily have gained entrance. One case had pneumonia and another septicæmia, in both of which the organisms could probably have been obtained from the blood. This leaves only two cases, or 3 per cent, without sufficient explanation as to the mode of infection. Of these, one case was a boy 19 years of age with bacteriuria, who had renal infection, while the other was a man of 78 years with bacteriuria who had cancer of the kidney.

Of the 21 women, only 7, or 33 per cent, had been catheterized. In the remaining 14, or 66 per cent, the bacteria probably gained entrance through the short urethral tract. Of the latter, 3 were girls aged 6, 7, and 21 years respectively; 2 cases followed painful coitus; two suffered from slight constipation; one had a tumor of the bladder; three were women 76 years old who had never been catheterized; one had hematuria; one had a stone in the right kidney.

His cases of pyelitis without cystitis are even more convincing. Of 21 cases, 16 were women and 5 men; of the 5 men, 2 had been catheterized or treated locally; 1 had a large prostate with complete retention; in only 2 cases out of the 5, or 40 per cent, was there no explanation as to the cause of the infection.

Of the 16 cases in women, there were 15, or 93 per cent, without any explanation as to the mode of infection.

Of Melchior's[20] 35 cases, 20 were men and 15 women.

Of the 20 men, 16, or 80 per cent, had been catheterized; 1 had tuberculosis; 1 was an old man with a large prostate who had incontinence; another had a large prostate with complete retention. This would leave only one case, or 5 per cent, without explanation as to the mode of entrance of the bacteria into the bladder.

Of the 15 women, 7, or 46 per cent, had been catheterized; 1 had tuberculosis; another was suffering from a typhoid cystitis. This would leave 6, or 40 per cent, without explanation as to the mode of entrance.

Escherich[21] reported 7 cases of cystitis in children between the ages of 6 months and 9 years, all due to the colon bacillus. Since all occurred in girls, and since several had a mild vulvitis, he concluded that it was most probable the bacilli entered through the short urethral tract.

Trumpp[22] reported 29 cases of cystitis in children from Escherich's clinic, of whom 21 were girls and 8 boys.

Suter[23] reported 118 cases exclusive of tuberculosis and gonorrhœal cystitis. He considered 35 of these endogenous, and 83 ectogenous or instrumental. Of the 35 endogenous cases, 15 were men and 20 women.

Of the 15 men in whom the infection is supposed to have occurred by the endogenous or descending route, one had gonorrhœa, stricture, and hypospadia; one had gonorrhœa with a very narrow stricture; one had gonorrhœa and prostatitis; one had prostatitis and epididymitis; one had epididymitis, large prostate, and residual urine; one was cystoscoped, after which procedure a severe cystitis followed; one had a cystotomy performed two years before for hematuria. All of these should be considered as ectogenous. This would leave 8 cases in which the histories are not complete enough to determine the route of infection, and as Alsberg[24] has said, not one of which is convincing in regard to the endogenous route.

Of the 20 women, only 2 were catheterized, leaving 18, or 90 per cent, without explanation as to mode of entrance.

Of his 83 cases classed under the heading of instrumental infections, only 5 were women.

Thus in his total of 118 cases 93 were men, in 87 of whom the origin of their cystitis was ectogenous, leaving only 6, or 6.4 per cent, without explanation as to the mode of infection.

In Brown's[25] series of 24 cases of chronic cystitis in women, 10 had never been catheterized, leaving 41.6 per cent without explanation as to route of infection.

To show how frequently women are infected, Albeck[26] reports the following cases: Of 150 non-pregnant women, 13 per cent had an infection of the urinary tract; in 392 pregnant women, 17 per cent had an infection; in 392 puerperal women, 14 per cent had an infection.

In Alsberg's series of 126 pregnant women, 12 per cent had an infection of the urinary tract; in 203 puerperal women, 29 per cent had an infection; in 41 cases of abortion, 17 per cent had an infection.

To summarize: In 192 men with cystitis or pyelitis, only 21, or 10 per cent, were without explanation as to the mode of infection; while in 129 women, 81, or 62 per cent, were without explanation as to the route of infection.

If there is a difference in the two sexes, it must be a local and not a constitutional one, and we find a ready explanation in the short and often relaxed urethral tract of the female.

Bacteria in the Normal Female Urethra.

The bacteria usually causing cystitis are inhabitants of the female urethra, the percentage varying according to the character of the cases examined and the methods employed. The colon bacillus has been found by all observers in from 12 per cent to 66 per cent of the cases. Recently Alsberg has found this bacterium in 100 per cent of the cases. He selected six cases of pregnancy and examined the urethra each day for twelve days. By taking *several loops of the secretion,* and plating on Drigalski-Conradi media, he found the colon bacillus in each case; if only one loop was taken, the results were not constantly positive on the successive days. He concludes that the colon bacillus is a regular inhabitant of the female urethra.

The differences in results obtained by different observers are due to the methods used; some wiped the lower portions of the urethra with bichloride and did not wash away the excess, others simply wiped the meatus with sterile cotton. The findings were also proportional to the amount of material used. Some used the loop, others used the straight wire. In many the differences were due to the media and the exactitude of the bacteriological methods employed.

The staphylococcus albus and aureus were found by different observers in percentages varying from 14 per cent to 90 per cent.

The bacteria of the urethra enter the bladder in two ways: They are introduced with the catheter, or they may enter directly from the urethra.

Any one reviewing the histories of the cases thus far reported and the percentages of cystitis following catheterization, will be impressed with the fact that catheterization is a very serious procedure, especially when local conditions are present such as trauma following gynecological operations and labor, pressure due to tumors or pregnancy, prolapse, retention, or paralysis.

The invasion of the bladder by microorganisms in the urethra is probably much more frequent than is usually supposed. The recent work of Albeck and that of Alsberg, who found infections of the urinary tract in 12 per cent out of a total series of 500 cases, seem to confirm this view. If a careful bacteriological examination were made in every case with mild bladder symptoms, we should find an ever increasing number due to the invasion of bacteria. This direct invasion from the urethra is favored by retention and incontinence, which produce a continuous column of fluid.

Nor is the male urethra a bar to the exogenous invasion of bacteria. The gonococcus does not seem to have any difficulty in invading the urethra and bladder. If the cases of non-gonorrhœal urethritis were examined carefully and the etiology determined, we should probably find the cause to be the bacteria which usually cause cystitis. The staphylococcus, streptococcus, and a diplococcus were found by Eitner.[27] The staphylococcus, colon bacillus, and an unrecognized diplococcus were found by Hume[28] in 11 cases examined. Other organisms found were the pseudodiphtheria bacillus, influenza bacillus, and the Friedlander bacillus.

2. The frequent existence of bacteriuria without infection of the ureters in cases which have never been catheterized.

Those who adhere to the endogenous route of infection refer to the fact that pyelitis, which is usually due to the colon bacillus, often occurs without any demonstrable lesion in the bladder.

Albeck has shown that in 150 non-pregnant women 13.3 per cent had bacteriuria, in 70 per cent of whom the bacteriuria was due to the colon bacillus. To determine whether the ureters were also infected he selected 13 cases and catheterized both ureters; in 8 cases the urine was clear and sterile from both ureters; in 3 no organisms were found on coverslips, and only a few colonies were found on the plates, which

he concluded were accidental; in 2 only were the bacteria in great numbers. He justly concludes that in a great majority of the cases the infection originates in the bladder.

We know that the bladder is very resistant to infection, and that the mere introduction of the colon bacillus will not produce a cystitis. If, however, the urethra or ureter is tied, a cystitis or pyelitis develops. All that is necessary to convert a bacteriuria into a pyuria is a retention. Such a retention is often produced during the second half of pregnancy, due to pressure on the ureters. Stone, trauma, or any of the accessory causes named above will produce the same result. If the retention or trauma affects the kidney, and not the bladder, a pyelitis develops without a cystitis.

The pathological and bacteriological studies of Schmidt and Aschoff (loc. cit.) of 16 cases of pyelo-nephritis confirm this view. They found that a microscopic examination usually gave the clue as to the route of infection. Where this failed, the microscopic examination supplied the information. The process always followed the tubules, and was ascending.

The preceding review thus shows that an ascending infection is of very common occurrence in women, and is also possible in men, when no instruments have been introduced into the bladder.

In the two cases reported in this paper the infection was an ascending one. In Case I the infection was limited to the bladder, since there was no pain in the region of the kidney and since there was no fever. The congestion and pressure caused by the pregnancy supplied the accessory factors enabling the organisms to invade the bladder.

In Case II (the husband) the infection certainly was an ascending one, since the infection started with a urethritis and since there was no fever until the infection reached the bladder. His symptoms started four days after the *acute* symptoms in his wife had developed, and were more severe, due possibly to the increased virulence of the organism which had passed through an intermediary host. The epididymitis must have been caused by the same organism, and extended by continuity along the seminal ducts as shown by the sequence of the location of the pain, and the gradual rise of the temperature. This case is particularly interesting in that it shows definitely an ascending infection of the bladder in the male by an organism other than the gonococcus. The general impression seems to be that unless instruments have been introduced, the infection of the bladder in the male must be by the blood route.

As a summary of this review, the following conclusions may be drawn:

1. The *B. lactis aerogenes* is a rare cause of cystitis.

2. The great majority of infections are due indirectly to the introduction of instruments.

3. Infections of the bladder, in cases where no instruments have been introduced, are very frequent in women and rare in men.

4. In infections of the bladder in women, without a history of the introduction of instruments, the route of infection is usually an ascending one and due to the direct invasion of the bacteria from the urethra.

5. Such direct invasion of the bladder also occurs in the male, and probably much more frequently than is usually supposed.

6. The introduction of a catheter or instruments into the bladder is a very serious procedure, since it may produce a pyuria if the local conditions are favorable, or a bacteriuria which later may be converted into a pyuria when the local conditions become favorable.

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COMBINED ADENOCARCINOMA AND MIXED-CELLED SARCOMA OF THE OVARY.*

By Ernest K. Cullen, M. B.,

Resident Gynecologist, The Johns Hopkins Hospital.

The association of malignant epithelial and connective tissue tumors in the same organ is well known. Carcinoma and sarcoma have frequently been found associated in the uterus. Each process has, however, been well defined and sharply differentiated from the other. The combination of these two processes in a single tumor is seldom observed. Much interest has been manifested in this combination since the work of Ehrlich[1] and Apolant on the transplantation of carcinomatous tumors in rats. From a purely carcinomatous tumor, they were, by repeated transplantation, able to procure a mixed tumor of carcinoma and sarcoma, and finally a tumor showing pure sarcoma. Their findings have been corroborated in Bashford's[2] laboratory. To use Bashford's words: "During transplantation of a rather slow growing adenocarcinoma with a somewhat fibrous stroma, a sarcomatous interstitial tissue has appeared in several separate strains. This has outgrown the carcinomatous elements in subsequent generations and given rise to a pure spindle-cell sarcoma." Isolated cases showing these combined processes have been reported. In 1904 Nebesky[3] reported a case of adenocarcinoma of the body of the uterus, showing a stroma of mixed-cell sarcoma. Taylor,[4] in 1909, reported a case of adenocarcinoma of the thyroid gland with a stroma of mixed-cell sarcoma, the latter process being the more vigorous.

A careful search of the literature for such a tumor occurring in the ovary has been unsuccessful. It was therefore deemed of sufficient pathological importance and interest to report in detail the following case:

Miss S., white, aged 50. Admitted to the Church Home and Infirmary in the service of Dr. T. S. Cullen, November 11, 1909. For several months she has had a great deal of pelvic pain and for the past two months has had considerable dysuria, necessitating frequent catheterization.

On pelvic examination, the cervix was found to be forward, the uterus back, and there was considerable edema of the vaginal vault, together with some slight induration. The pelvis and lower abdomen were filled by a rather tender hard tumor mass. There was strong suspicion of malignancy, so an immediate exploratory operation was indicated.

Operation, November 13, 1909. When the patient was examined under ether it was deemed advisable to do a pelvic puncture. A considerable quantity of free fluid and a great deal of blood were obtained, but there was no diminution in size of the tumor mass. The abdomen was at once opened and the large mass felt on ether examination found to be a malignant growth of the left ovary. The bladder was drawn high up over the tumor and adherent to the posterior surface; thus accounting for the dysuria and the necessity for catheterization. The tumor, together with the uterus and appendages from the opposite side, was removed as rapidly as possible. During removal it was found that the right ureter was densely adherent to the tumor and there was involvement of the peritoneum in the right side of the pelvis. The right ureter was dissected free by splitting the anterior part of the broad ligament, which enabled the operator to expose the ureter with considerable ease. Fully one-third of the pelvic peritoneum was removed with the tumor, and as far as could be seen macroscopically, no malignant tissue was left. An iodoform drain was placed down through the pelvis.

The patient made an uneventful convalescence.

Gyn. Path. No. 14414. *Pathological Report.*—The specimen consists of a uterus which has been removed supravaginally, together with a mutilated mass of tissue representing the appendages from the right side and a solid tumor of the ovary from the left side. Attached to the tumor is the left tube.

The uterus, apart from adhesions laterally, shows nothing abnormal. The right tube and ovary are bound in adhesions and the ovary is cystic. Fig. 1.)

The ovarian tumor in its present flattened condition measures 15 x 14 x 7 cm. It is generally smooth on the surface but in a few places old tags of adhesions are present. It has been attached by a pedicle about 3 cm. in diameter. Coursing over the tumor and attached to it by thin mesosalpinx is a tube, which has been converted into a hydrosalpinx. The surface of the ovarian tumor is somewhat irregular and nodular. It is greyish-yellow in color and numerous congested vessels are visible upon the surface. These vessels are most prominent in the valleys between the slightly nodular elevations. On section the tumor is found to contain a central shallow cavity measuring 5 x 9 cm., and at one point near the periphery it reaches a depth of 2 cm. (Fig. 2.) The floor of this cavity is smooth and is lined by a thin yellowish-white fibrillated membrane. It resembles very much a markedly enlarged kidney pelvis. Surrounding the cavity and occupying the space between it and the cortex are irregular lobulated areas which are greyish-yellow in color and in places present a finely granular honey-combed appearance. (Fig. 2, *a.*) In some places distinct hemorrhagic areas are visible and in others there is simply a brownish coloration of the tissue. At other points about the periphery are irregular firm whitish areas varying from 8 mm. to 2 cm. in diameter. (Fig. 2, *c, g, e.*) In some places these areas show evidence of breaking down with slight cystic formation. The picture presented is a distinctly malignant one. In some places the tissue appears carcinomatous, in others it resembles sarcoma.

Gyn. Path. No. 14414. *Microscopic Examination.*—Sections were taken from eight different portions of the tumor, representing every gross type of pathological process present. The tumor is found to consist of a well-defined adenocarcinomatous process and an equally well-defined sarcomatous one. In certain parts of the tumor these two processes are side by side. In others there is pure sarcoma with absence of any carcinoma. In still other parts are found areas where there is well-defined carcinoma and a rather cellular and suspicious looking stroma; the stroma, however, not showing the typical picture of sarcoma seen elsewhere. In those sections showing the combined processes, the

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* A report of the original tumor was made before the Johns Hopkins Hospital Medical Society April 18, 1910.

[1] Ehrlich, P., and Apolant, H.: Berl. klin. Wchnschr., 1905, XLII, 871.

[2] Bashford and Haaland: Imperial Cancer Research Fund. (Third scientific report.) London, 1908, 248.

[3] Nebesky: Arch. f. Gynäk., 1904, LXXIII, 653.

[4] Taylor: J. Path. and Bacteriol., 1908, XII, 440.

carcinomatous one is marked by large islands of glands (Fig. 3), the glands in most instances being irregular in size and shape and presenting a distinctly atypical appearance (Fig. 4). The individual cells vary in size, shape, and staining qualities, and many nuclear figures are visible. Immediately adjacent to these islands of glands, the stroma shows a distinctly malignant appearance. The predominating cells are spindle-shaped and round, but there are many large irregular, deeply staining cells scattered throughout (Figs. 3 and 4, *d*). Some parts of the tumor show a greater number of these large cells than do others. The individual stroma cells vary in size and shape. The nuclei are as a rule large, stain rather deeply, and assume an oval or round contour. The protoplasm of the cells takes a fairly uniform stain. The large (atypical giant) cells assume different sizes and shapes. (Figs. 3 and 4, *d*.) The nuclei are irregular in outline, multiple, very deeply stained, and are surrounded by a considerable quantity of protoplasm. A number of nuclear figures are visible. The carcinomatous and sarcomatous processes are entirely distinct and independent and this point is especially well emphasized by the fact that the glands of the carcinoma have retracted from the stroma and there is a distinct area of separation between the two. The cells which line the narrow spaces that separate the carcinomatous from the sarcomatous processes are in the main uniform in appearance and seem to form a distinct membrane. In some portions of the tumor there is marked degeneration. Here the tissue has undergone extensive hyaline change and merely shadows of cells are present. Sections taken through the periphery show a well-defined capsule, which has undergone partial hyaline degeneration, and considerable infiltration with round cells. At no point was there evidence of penetration by either malignant process. The vascularity of the tumor, while not especially prominent, is in greater evidence where the sarcomatous process is most active.

The right ovary on microscopic examination shows no evidence of malignancy. Both tubes show some chronic inflammation, but there is no involvement by the malignant process. Sections from the body of the uterus show an early diffuse adenomyoma. The cervix is quite normal.

From the tumor it is impossible to determine whether one process preceded the other or whether the development was simultaneous. It is significant, however, that in those areas where the carcinomatous elements show the greatest disintegration the sarcomatous process presents a wilder and a more rapidly growing appearance. Degeneration seems to play some rôle in the early development of sarcoma in certain instances. This point has been emphasized by Kelly and Cullen [5] in their examination of myomata which have undergone sarcomatous transformation. In many instances the sarcomatous tissue was adjacent to hyaline degeneration on the one side, and fairly typical looking myomatous tissue on the other. Bashford (*loc. cit.*) states: "In all the latter stages of sarcoma development we find the first changes beginning in the center of the carcinomatous tumor where sclerotic changes are present."

RECURRENCE OF TUMOR IN PELVIS.

Within a few weeks after leaving the hospital, there were signs of a recurrence of the tumor in the pelvis and the patient died on October 27, 1910, eleven months after the operation.

Autopsy Report.—(The body had been embalmed with a weak formalin solution about ten hours before the post mortem examination.) The body is markedly emaciated and the skin shows a diffuse yellowish tinge. There is some abdominal distension, due partially to fluid, but no edema of the extremities is present. On opening the abdominal cavity, there is found to be some distension of the bowel and about one liter of free fluid, with a distinctly formalin odor. The viscera have been partially hardened. Occupying the pelvis is a large semi-cystic mass which is intimately adherent to the sigmoid, rectum, bladder and pelvic wall. Scattered everywhere over the surface of the large and small bowel are numerous firm whitish nodules varying in diameter from 1 mm. to large confluent patches approximately 7 cm. in diameter. Sections through the affected portion of the bowel show the process to be limited to the outer coat. The omentum is markedly thickened and is studded with numerous large and small firm white nodules, similar to those on the bowel surface. The liver, spleen and kidneys are slightly enlarged, but show no evidence of metastases. Both lungs are edematous and a few scattered areas of broncho-pneumonia are present. Careful examination showed no evidence of metastases outside of the peritoneal cavity, no enlarged retroperitoneal glands were found.

Anatomical Diagnosis.—Pelvic tumor, general peritoneal metastases, broncho-pneumonia.

Gyn. Path. No. 15613. *Pathological Report.*—The tumor mass measures approximately 15 x 12 x 12 cm. It is cystic in character and is covered by many old adhesions. On section are found numerous cystic spaces, the largest of which is approximately 8 cm. in diameter. These contain some light straw-colored fluid and are lined by a shaggy tissue which is readily peeled off. The walls, which vary in thickness from 0. 5 to 5 cm., consist of a moderately soft homogeneous tissue, pinkish-white in color, closely simulating sarcoma.

Histological Examination.—As in the original tumor the two processes are combined, but the sarcomatous elements predominate. Scattered throughout a bed of sarcomatous tissue are groups of glands presenting the typical picture of adenocarcinoma (Fig. 5). The sarcoma belongs to the mixed-cell type, the spindle cells predominating. Numerous large, so-called giant cells, are present. These are well seen in Fig. 6. In some sections the picture was one of pure sarcoma, no glands being visible (Fig. 6). The metastases on the bowel wall and in the omentum show a picture of adenocarcinoma (Fig. 7). The stroma shows no evidence whatever of sarcoma.

Study of the original tumor shows a combination of the two malignant processes, the carcinomatous elements predominating. In the recurrent tumor, however, the process is mainly sarcomatous in character.

It is interesting to note that metastases were purely carcinomatous. They were limited to the peritoneal surfaces of the bowel and the omentum, simulating in great measure the picture observed in malignant papillocystomata of the ovary with general peritoneal implantations.

I am indebted to my brother, Dr. Thomas S. Cullen, for the privilege of reporting this case and to Dr. J. S. Bloodgood and Mr. Schapiro for the protomicrographs.

The patient was referred to Dr. Cullen by Dr. Clara Eirley, of Hagerstown, Md.

DESCRIPTION OF FIGURES.

Fig. 1. —Gyn. Path. No. 14414 (natural size). This picture represents the appearance of the ovarian tumor which has been hardened in 10 per cent formalin.

Fig. 2.—Gyn. Path. No. 14414 (natural size). On section of the tumor various stages of cystic and hyaline degeneration are visible. *b* represents a large central cavity lined by a slightly

[5] Kelly-Cullen. Myomata of the Uterus. W. B. Saunders Co., 1909, 175.

FIG. 1.

FIG. 2.

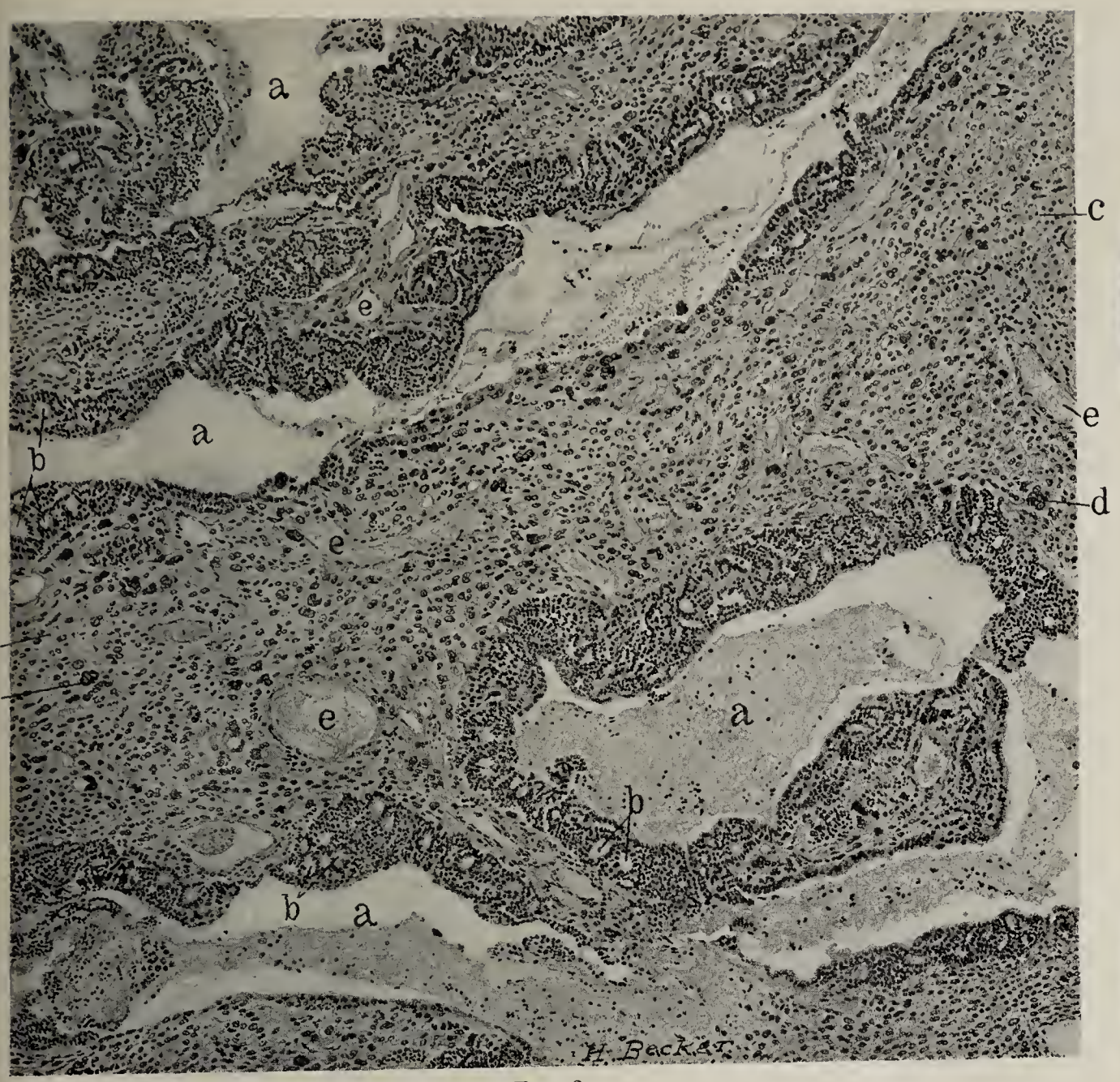

FIG. 3.

FIG. 5.

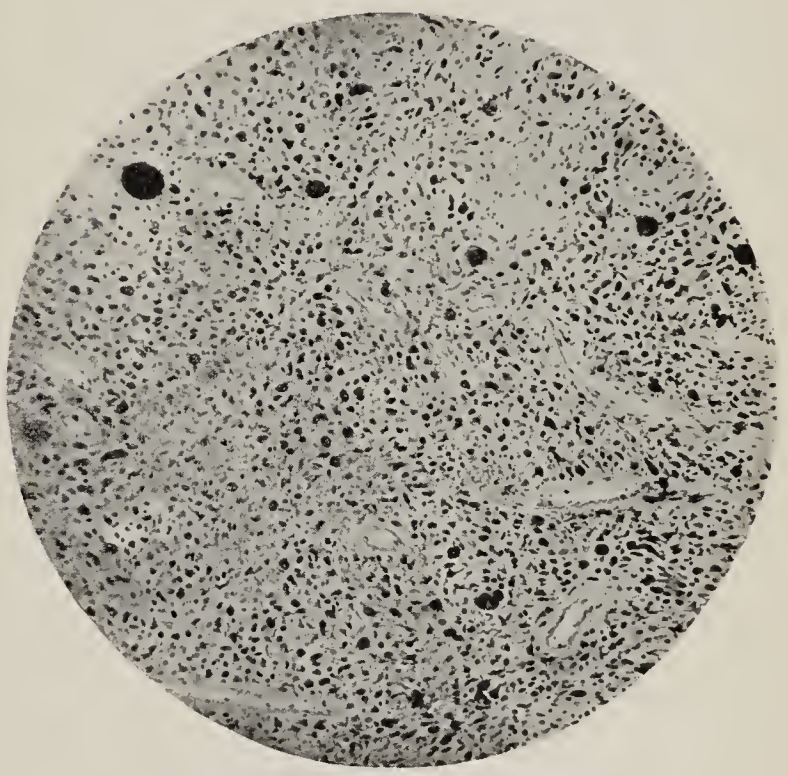

FIG. 6.

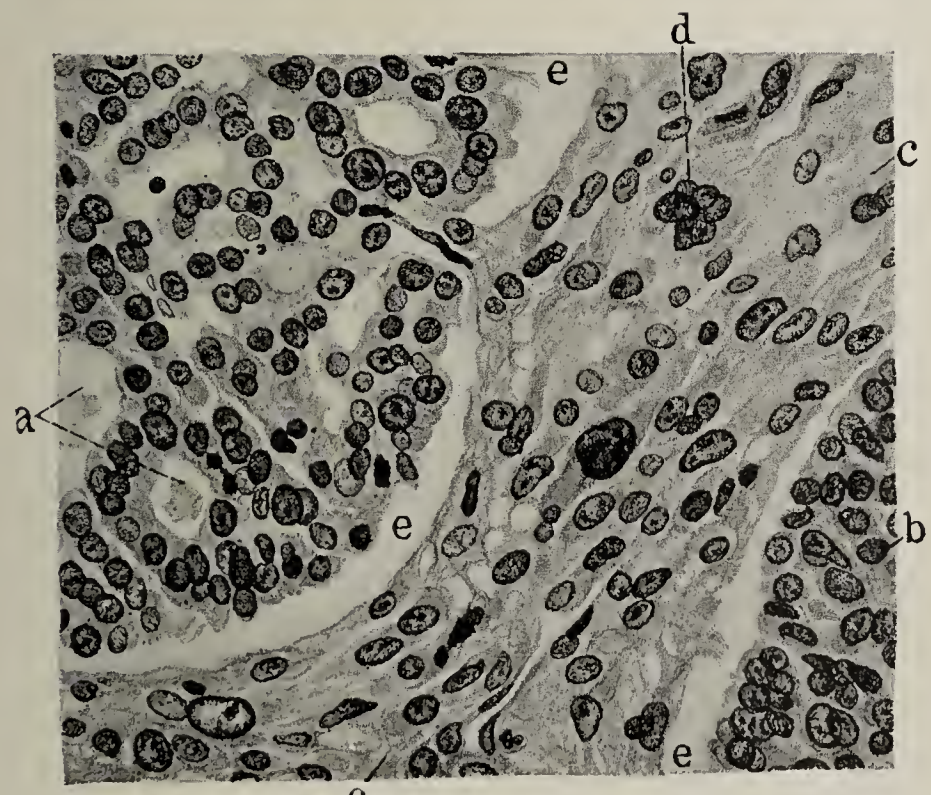

FIG. 4.

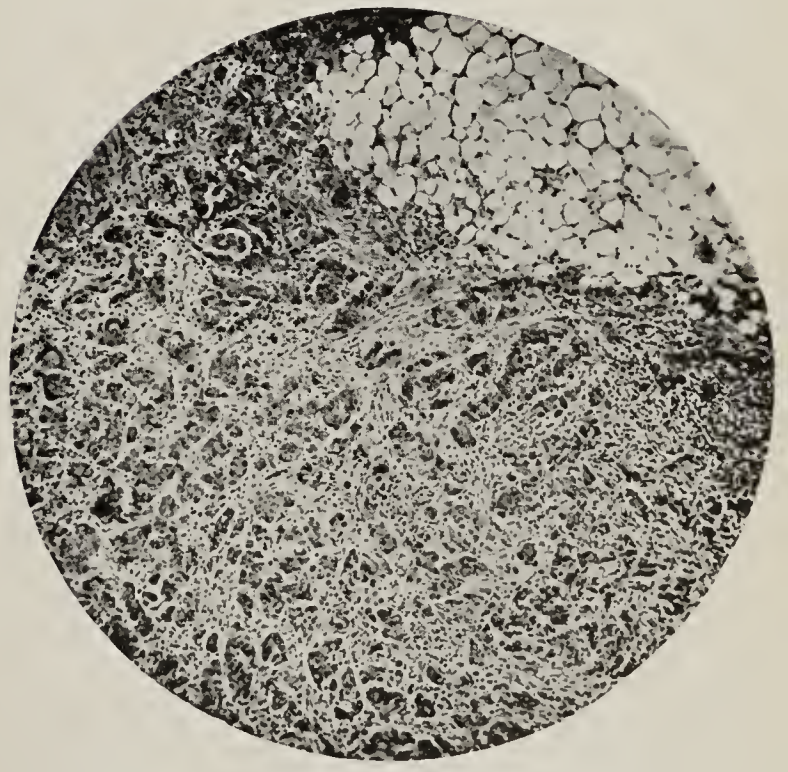

FIG. 7.

shaggy membrane. Small cystic spaces are scattered throughout the tumor. At *a* is seen the fine honey-combed appearance. At *c*, *d*, *e* and *g* the tissue is fairly homogeneous and looks like sarcoma. *f* is a small blood vessel.

FIG. 3.—Gyn. Path. No. 14414 (80 diameters). The two processes are well represented here. At *a* are seen the large gland lumina partially filled with coagulated fluid. The glands present the typical picture of adenocarcinoma. The stroma *c* shows a decidedly active and malignant picture. The majority of the cells are spindle shaped, but numerous large irregular cells, *d*, are found scattered throughout. The stroma is rich in blood vessels *e*.

FIG. 4.—Gyn. Path. No. 14414 (380 diameters). This illustration shows a magnification of the picture seen at Fig. 3, *b*. Note the large atypical cells lining the glands *a*. At *b* the glands are much less well defined. The stroma *c* consists of cells irregular in size, shape and staining qualities, and at *d* is shown a large so-called giant cell. Note the spaces *e* between the carcinomatous and sarcomatous processes, showing a tendency on the part of the carcinoma to retract from the sarcoma.

FIG. 5.—Gyn. Path. No. 15613. The section here pictured is taken from the recurrent tumor. The combined malignant processes are well marked. The sarcoma predominates and appears much more active than the process in the original tumor (Fig. 3).

FIG. 6.—Gyn. Path. No. 15613. This section shows a portion of the recurrent tumor which is purely sarcomatous in character. Note the number of large atypical cells.

FIG. 7.—Gyn. Path. No. 15613. This shows a section through the thickened and nodular omentum. The adenocarcinoma is well marked. The stroma shows no evidence of sarcoma.

THE BLOOD-PICTURE IN HODGKIN'S DISEASE.

By C. H. BUNTING, M. D.

(*From the Pathological Laboratory of the University of Wisconsin.*)

The blood-picture of Hodgkin's disease, as manifested in the various published cases, has been critically considered by Fabian[1] in a recent article, and his findings are summarized as follows:

(1) The most frequent blood-picture found in the course of Hodgkin's disease is a polymorphonuclear neutrophile leukocytosis of moderate grade.

(2) The blood-picture may be unmodified (about one-fifth of all cases).

(3) In about one-fifth of the reported cases there is a more or less well marked leukopenia, either present throughout the entire course, or transitory, and if the latter occurring more frequently in late stages.

(4) Qualitatively, the blood shows a relative neutrophile leukocytosis—that is, an increase in percentage up to 99 per cent and more; with a corresponding decrease in lymphocyte percentage to 3 per cent and, in two cases, to practically 0 per cent; most frequently at the same time with an absolute leukocytosis, at times with a leukopenia and, rarely, with a normal count.

(5) In about one-fourth of the cases there was an eosinophilia, usually slight or moderate, seldom of marked degree.

(6) Very seldom one may find a mastzell increase.

(7) Scattered myelocytes were noted—very rarely enough to estimate.

(8) In one case an enormous increase in blood-platelets was noted.

(9) At times, though usually transitory, a slight, rarely a marked, lymphocytosis may be noted.

(10) In the course of the disease there develops a secondary anæmia, at first moderate, but later pronounced.

Fabian's general conclusions from his study of these cases is that while there may be characteristic features of the blood-picture in Hodgkin's disease, they are not constant enough to be of diagnostic value, and that in further study an attempt should be made to correlate the blood picture and that found in the glands. During the past three years the author has been making such a study in conjunction with Dr. J. L. Yates, of Milwaukee, and, while his findings are in general in agreement with those of Fabian, yet, on the other hand, they are sufficiently at variance to seem to warrant publication. There are two features of this study which may be emphasized, and which add to its value. In most of the cases at least one blood count has been made just previous to the removal of a gland for section, and further, all the smears have been examined by one person, the author, who has used the same staining and counting technique throughout.

In a previous paper[2] I have emphasized one of the most marked characteristics of the blood smears of Hodgkin's disease, that is, the presence of a large number of blood-platelets, inclusive of unusually large platelet forms, practically megalokaryocyte pseudopodia. This has been observed in all the eleven cases forming the basis of this report, both in early and in late cases, and over considerable periods of time in cases on which blood counts have been made at intervals.

From this constant finding and from pathological findings in autopsy material from cases of Hodgkin's disease, it was suggested in the previous report that the toxin of the disease acted as strongly upon the platelet-forming elements as upon the lymphocytes. An eventual necrosis of megalokaryocytes in the bone-marrow was found. One might have predicted from this finding that in late cases an exhaustion of platelets might take place, resulting in a low platelet count in the circulation. Such a case had not occurred in the author's series at the time of publication of his first report, but since then Case V of the series has shown such a change. After

[1] Wiener klin. Wchnschr., 1910, XXIII, 1515; Centralbl. f. allg. Path., 1911, XXII, 145.

[2] Johns Hopkins Hosp. Bull., 1911, 114.

having shown a high platelet content of his blood in counts at intervals from November 9, 1909, to September, 1910, the boy returned to the Columbia Hospital, Milwaukee, in April, 1911 with serious hæmorrhages from the mucous membranes, with a secondary anæmia, a leukopenia—3500 to 4000—and fewer platelets than leukocytes, as shown by repeated examinations made during April and May. However, while exceptional or terminal cases may show this platelet exhaustion, the excessive number would appear to be constant in the course of the disease.

Coincident with this platelet study, careful study of the leukocyte picture in the disease has been made and has led to the conclusion that in the combined platelet and leukocyte picture one has features that are very characteristic and, in fact, almost pathognomonic of Hodgkin's disease. While from my experience I believe that the diagnosis may be made from examination of the blood smear, I would not recommend the method to the exclusion of the histological examination of an excised gland. The latter method is too simple to neglect, but, where glands are inaccessible, or where permission for removal is not obtained, the examination of blood smears is very helpful, and is especially convincing if backed by a negative von Pirquet reaction.

In this study, blood smears from eleven cases of Hodgkin's disease have been carefully examined and differential counts made. In a few cases several counts have been made at intervals of some months, giving confirmatory evidence of the value of the picture. The cases have varied in their stage of development from early cases to those a few months from the fatal termination, so that it has been possible to note the changes which take place in the blood-picture with the development of the disease.

The blood smears have been stained with Wright's stain for the purposes of the counts, although Ehrlich's triple stain has been used for the determination of certain features. Five hundred cells have been the routine and the smallest number counted, but in some cases this has been exceeded. The leukocytes have been grouped into seven classes, except in a few of the early counts where but six were made. These groups are: (1) Polymorphonuclear neutrophile (N.); (2) Eosinophile (E.); (3) Basophile (mastzell) (B.); (4) Small lymphocyte (S. L.); (5) Large lymphocyte (L. L.); (6) Large mononuclear (L. M.); (7) Transitional (Tr.).

While the first three groups need no explanation, a word may be due as to the divisions of the so-called mononuclear or non-granular groups. Study of blood smears from normal individuals, stained with the Romanowsky stains, shows four distinct types of mononuclear cells. However, in studying large numbers of these cells, one finds that the distinctions in size and staining reaction are not always sharply made; that is, the groups overlap somewhat, so that the separation becomes more or less arbitrary. This is especially the case in regard to the small and large lymphocyte groups, and in regard to the large lymphocyte and the large mononuclear. In the earlier counts the last two groups were included under a single head. Although this grouping may be artificial and arbitrary, the same standards were employed throughout in forming a judgment, and the separation may be of some value.

The groups are characterized as follows:

(1) *Small Lymphocyte.*—A cell with deeply staining nucleus, which scarcely exceeds a red-blood cell in diameter, and with a scant rim of basophilic protoplasm.

(2) *Large Lymphocyte.*—A cell usually almost the size of a neutrophile leukocyte with nucleus larger than that of the preceding class, and with protoplasm more abundant, less basophilic as a rule, and containing numerous coarse, oftentimes almost rod-like metachromatic granules.

(3) *Large Mononuclear.*—A cell larger than a neutrophile leukocyte, with large round or oval nucleus and considerable protoplasm, staining a fairly deep blue and containing at times a few fine metachromatic granules.

(4) *Transitionals.*—The largest cells of the groups, with nuclei of various shapes, from simple indented nuclei, to lobed, mulberry-shaped, or even ring-shaped nuclei; and with abundant clear, light-blue protoplasm thickly dotted with fine metachromatic granules which do not stain with Ehrlich's triple stain.

As the transitional leukocyte forms a prominent feature of the differential picture in Hodgkin's disease, a further word in regard to it seems necessary. It is quite evidently misnamed, for it bears no relation to the polymorphonuclear neutrophile. To one "brought up" medically on the Ehrlich stain, this cell as revealed by Wright's stain comes as a surprise. With the Ehrlich stain, the nucleus is but faintly stained and its structure is poorly brought out, while the protoplasm usually appears as an unstained halo, or with but a slight tint and with but an occasional granule. With Wright's stain, however, the nucleus stains sharply. It is massive and of a protean variety of shapes—knobbed, lobed, twisted, folded, ring-shaped. So complex are the nuclei, at least in Hodgkin's smears, that one is at first inclined to believe he is dealing with a foreign cell. Yet the cell is present in normal smears to the extent of from 6 to 8 per cent of the leukocyte count, and the nuclei appear almost if not fully as complex as in Hodgkin's smears. The protoplasm of the cell stains a clear blue and is crowded with fine azure granules finer than those of the neutrophile leukocyte. They are finer also than the platelet granules, but have the same tint. As noted above, they are unstained by the Ehrlich stain. I do not desire to discuss the relation of the transitional cell to other cells or to enter into the question of its origin, further than to say that cells morphologically and tinctorially similar may be found in smears from normal lymph glands.

Preliminary to the detailing of the blood counts in the Hodgkin's cases examined, it should be said that all of the smears, with the exception of the late ones in Case V, showed very abundant platelets and in every case also large platelet forms and pseudopodia were present. The leukocyte examinations and the brief clinical points necessary, follow:

CASE I (Dr. Yates).—November 20, 1908. Male, white, 21. Onset of disease, July, 1908. Cervical and axillary glands involved. Test gland removed October 30, 1908, showed early Hodgkin's changes. Gradual improvement under treatment. Blood counts:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L L.		L.M.	Tr.
XI. 20, '08.....	5,304,000	7,500	51.2	3.2	1.6	25.4		10.		8.6
III. 4, '09.. ..	4,968,000	4,800	55.2	2.4	0.8	23.6		6.6		11.4
VI. 11, '09.....	5,600,000	7,000	65.8	2.8	0.0	16.8	7.6		1.2	5.8
II. 16, '10.....	5 800,000	7,000	59.8	4.0	1.4	15.4	8.8		1.8	8.8
VI. 9, '11.....	.....	8,500	65.0	2.6	1.2	21.2	3.		0.6	6.4

CASE II (Dr. Yates).—Male, white, 10. Large mass of discrete glands in left cervical region of at least one year's duration previous to removal, November 10, 1908. Glands show well-marked Hodgkin's picture. Von Pirquet reaction negative October 8, 1910. Gradual improvement under treatment. Blood counts:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L. L.		L.M.	Tr.
IV. 1, '09.....	4,712.000	9,500	56.2	8.6	0.4	16.4		7.4		11.0
I. 22, '10.....	5,250,000	9,600	63.6	3.6	0.0	12.0	12.0		2.0	6.8
III. 12, '10.	.....	.....	53.4	5.2	1.0	13.	16.		1.6	9.8
X. 8, '10.....	4 960,000	9,800	53.2	5.2	0.4	27.8	4.		1.4	8.

CASE III.—April 1, 1909. Male, white, 30. Seen 2 weeks after second operation for glands of neck. First operation 6 months previous at Rochester. Diagnosis, Hodgkin's disease. Blood counts:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L. L.		L. M.	Tr.
IV. 1, '09.....	4,560,000	10,000	79.4	0.2	0.4	5.8		3.4		10.8

CASE IV (Dr. Tupper, Eau Claire, Wis.).—February 5, 1910. Female, white, 40. Onset, — months previous in right inguinal glands. Subsequent involvement of left inguinal, left axillary, left and right cervical glands. Test gland shows well-marked active Hodgkin's picture. Death in October, 1910. Blood count:

Date.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
II. 5, '10.....	36.	0.6	0.2	39.2	10.6	2.8	10.6

CASE V (Dr. Yates).—November 9, 1909. Male, white, 8 years. Enlargement of cervical glands began 5 months previous to date. Left inguinal glands also enlarged. Test gland, November 30, 1909, shows hyperplastic stage of lesion. January, 1910, cervical glands removed. October, 1910, von Pirquet test negative. April, 1911, mucous membrane hæmorrhages, anæmia. Blood counts:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L. L.		L. M.	Tr.
XI. 9, '09.....	.....	9,900	59.4	4.6	0.4	21.8		3.6		10.2
XI. 30, '09.....	.....	.....	50.8	5.8	0.6	26.8		7.2		8.8
II. 26, '10.....	5,000,000	5,000	55.2	1.4	0.4	22.4	9.2		2.0	9.4
IX. 7, '10.....	5,160,000	8,700	59.4	1.	1.2	16.4	6.6		5.	10.4
IV. 21, '11.....	3,456,000	4,800	63.2	1.8	1.	10.2	4.6		1.4	17.8
Transfused.										
IV. 24, '11.....	3,176.000	3,800	54.	6.8	0.2	17.8	4.8		1.8	14.6
V. 2, '22.....	2,624 000	8,300	67.6	1.4	1.4	6.8	9.6		0.6	12.6
Transfused.										
V. 5, '11.....	2,760.000	4.500	54.6	2.6	2.	18.8	7.6		0.6	13.8
V. 9, '11.....	3,200,000	4,000	50.8	4.	1.6	25.8	6.4		0.6	10.8
Transfused.										
V. 10, '11.....	.....	..	60.	9.8	0.6	8.2	6.8		0.4	14.2
V. 13 '11.	3.400.000	3.500	56.2	4.8	0.8	17.6	6.4		0.4	13.8
V. 22, '11.....	3,712,000	3.400	55.8	3.2	0.0	19.8	3.6		1.2	16.4
V. 29, '11.... ..	3,680,000	3,600	56.4	3.4	1.6	18.	8.1		0.6	11.8

CASE VI (Dr. Sullivan, Madison, Wis.).—March 1, 1910. Male, white, 16. Left cervical glands much enlarged. Marked induration of neck. Enlargement noted for only 1 month, but the amount of sclerosis in test gland suggests greater duration. March 10, wound resulting from removal of gland for diagnosis still unhealed. May 13, wound healed but induration of neck marked. Blood counts:

Date.	W.b.c.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
III. 10, '10.....	18,000	81.6	0.6	0.4	4.2	3.	1.6	8.6
V. 13, '10.....	27,000	80.6	1.6	0.0	7.8	2.8	0.8	6.4

CASE VII (Dr. Bennett, Oregon, Wis.).—January 5, 1910. Female, white, 64. In October, 1909, general glandular enlargement with clinical diagnosis of Hodgkin's disease. Death June 30, 1910. Blood count:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
X. 24, '09.....	3,200,000	4,480							
I. 5, '10.....	.....	.....	54.8	4.2	0.4	20.0	9.8	1.6	9.2

CASE VIII (Dr. Yates).—Male, white, 33. Onset in March, 1907, with supraclavicular glandular enlargement. In September, 1908, supraclavicular and left axillary glands most enlarged. Some enlargement of right cervical, axillary and inguinal glands. October 30, 1908, excised gland shows typical and advanced Hodgkin's disease. Death occurred May 20, 1909. Blood count:

Date.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
I. 10, '09.	76.2	1.4	0.6	7.6	6.0		8.2

CASE IX (Dr. Yates).—October 3, 1910. Male, white, 5. Marked enlargement of left cervical glands of 5 months duration. Test gland shows well-marked Hodgkin's changes. Death from shock at operation. Blood count:

Date.	R. b. c.	W.b.c.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
X. 3, '10.....	5,160 000	4,200	54.4	2.4	0.2	22.6	8.6	2.4	9.4

CASE X (Dr. Yates).—Male, white, cervical Hodgkin's. Count made 2 months previous to death of patient.

Date.	W.b.c.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
IV. 30, '10.....	14,300	84.	0.0	0.0	3.8	1.0	1.0	10.2

CASE XI (Dr. Baird, Eau Claire, Wis.).—December 8, 1910. Male, white, 22. Enlargement of supraclavicular gland noted one year previous. Axillary glands enlarged at date. Test gland shows definite Hodgkin's picture. Blood count:

Date.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
XII. 8, '10.....	81.8	0.2	0.6	2.6	2.6	1.	11.2

When one examines these counts critically in an attempt to correlate the counts with definite stages of the disease process, he is confronted with difficulties arising from the facts that all parts of the lymphoid tissue are not affected, and further, that, of any large group of glands affected by the disease, the individual glands may show different stages of development of the process. Yet there are some points in the counts which stand out definitely. The most striking feature perhaps is the constant high percentage of the so-called transitional cells. This high percentage occurs not only when the total leukocyte count is approximately normal, but also is maintained even when there is a sharp leukocytosis. With a normal total count of leukocytes the percentage of transitionals approximates 10; with a very marked leukocytosis, as in Case VI (27,000), one may have a reduction (6.4 per cent); while in a leukopenia, as in Case V, the percentage rises to 17.8 in a total of 4800. The series indicates, then, that throughout the disease there is a relatively large number of these cells in the circulation. When one recalls that similar cells are found in smears from normal lymph glands, and also that in Hodgkin's disease there is a marked proliferation of the endothelial elements of the glands, it is difficult not to draw the conclusion that such a proliferation results in this excessive transitional content of the blood. Such a suggestion, however, cannot be considered as proved.

The lymphocyte count has varied much in these cases, but there is a definite tendency for a percentage decrease from a normal or slightly increased count in early and active stages to a very low count in later stages. Thus in Case IV we find

49.8 per cent of small and large lymphocytes in an active phase; in Case V, 31.6 per cent; in Case IX, 31.2 per cent. On the other hand, in the advanced cases, X, XI, III, we find from 4 to 8 per cent.

With this decrease in lymphocyte percentage, we find a corresponding increase in the polymorphonuclear count, from a relatively normal count during the course of the disease, to a relatively high count (76.2, 79.4, 81.8, 84 per cent) in the terminal stages or when the periglandular infiltration and induration are marked. The neutrophiles appear therefore to be unaffected except by extra-glandular processes and not by the changes taking place within the glands themselves.

Quite the opposite is the relation of the disease to the eosinophile. Eosinophiles are found in the glands in large numbers. Remembering that the count of cells in the peripheral blood represents but the ratio of supply to demand, it is not surprising to find very low counts of eosinophiles during the active progress of the disease (0.6 per cent or less in six of the cases). In reactive or quiescent cases, however, the count is higher, either toward the upper limit of normal, or slightly above. The highest count found was 8.6 per cent in Case II, if one excepts the 9.8 per cent found in Case V twenty-four hours after transfusion. If, as seems probable to the author, from a study of lymph glands at autopsy in a variety of conditions, the products of destruction of lymphocytes are positively chemotactic for eosinophiles, and if the findings above are not exceptional, the eosinophile count in cases of Hodgkin's disease would seem a good index of the progress or activity of the disease.

There is no striking change in the basophile count, or in that of the large mononuclears.

While these deviations of the Hodgkin's blood-picture from the normal are pronounced, the question naturally arises as to how they compare with counts in other diseases of the lymph glands. My series of counts in other conditions is not large, but in none of the conditions have I found the combined platelet-leukocyte picture that has been found in Hodgkin's disease.

In tuberculosis of the gland the platelet count is high, but in smears from four cases I have not found the large forms which are common in Hodgkin's. The transitional leukocytes are on the upper limit of normal or slightly above. The four differential counts are as follows:

	W.b.c.	N.	E.	B.	S. L.	L. L.	L.M.	Tr.
1.....	9,000	41.6	2.4	0.0	43.2	4.4	0.4	8.
2.....	.....	56.	1.8	0.2	26.4	5.	3.	7.6
3.....	.....	63.	1.2	0.6	19.	6.	2.2	8.
4.....	.....	64.8	1.8	0.2	19.4	6.	1.	6.4

In two cases of relatively acute non-specific lymphadenitis following throat infections, the following differentials were obtained:

	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
1..... ...	72.2	0.2	0.2	14.6	2.2	1.8	8.8
2.....	47.8	4.	0.6	30.6	5.4	1.6	10.8

In these one finds quite the picture seen in active and early stages of Hodgkin's disease as far as the leukocytes are concerned. This is what one might expect, if the analysis of the Hodgkin's picture given above is correct. In both of these cases the striking platelet-picture of Hodgkin's disease was lacking.

Finally, in one case of chronic simple sclerosis of the lymph glands of obscure origin, there was obtained the following count, with a low number of blood-platelets:

N.	E.	B.	S. L.	L. L.	L.M.	Tr.
72.	10.0	0.8	11.8	1.4	0.4	5.6

These counts are too few to establish a blood-picture for the various conditions, yet they do not vitiate the general conclusions of the author from his study of Hodgkin's disease, that the blood-picture is characteristic, is indicative of what is transpiring in the glands, and may be, if carefully weighed, a help in diagnosis.

THE TRANSPLANTATION OF FREE FLAPS OF FASCIA.

AN EXPERIMENTAL STUDY.

By John Staige Davis, M. D.,

Instructor in Surgery, The Johns Hopkins University.

(From the Hunterian Laboratory of Experimental Medicine, The Johns Hopkins University.)

Introduction.—For some time I have been interested in the methods brought forward for replacing and for reenforcing weakened or defective tissues, and while some of the methods are admirable, all are limited in their application. It seemed worth while to search for a material which would accomplish the same purpose but would have a wider field of usefulness.

In looking about for some suitable tissue in the body which was easily obtainable, which had considerable strength, and at the same time was sufficiently flexible for any desired need, I was led to try the experimental transplantation of free flaps of fascia.

After proceeding with the experiments for sometime I found that some excellent work had already been done along this line.[1] However, my results were sufficiently suggestive to warrant a report on the subject, in order to again call attention to this promising surgical procedure.

[1] Kirschner, M.: Ueber freie Sehnen- und Fascien Transplantation. Beitr. z. klin. Chir., 1909, LXV, 472.

Günther: Ueber Duraplastic: eine klinisch-experimentelle Studie. Beitr. z. klin. Chir., 1910, LXIX, 740.

Hohmeier: Ueber ein neues Verfahren zur Deckung von Trachealdefekten. München. med. Wchnschr., 1911, LVIII, 948.

Since this paper was handed in for publication the following

Sixty-two experiments were done on thirty-nine dogs. Ether anesthesia was used in each experiment.

Technic.—The part was shaved, washed with green soap and water, then with alcohol and ether. After the skin was thoroughly dry it was painted with tincture of iodin, 2.5 per cent. The iodin solution was also freely used in the open wounds and after suture of the skin.

Fine black silk was the ligature and suture material used throughout. The wounds were closed in layers wherever possible. The skin was closed in every instance with the buttonhole stitch.

Dry sterile gauze secured by a bandage was used wherever dressings were applied.

The fascia was obtained, for the most part, from the thigh, the ilio-tibial band of the fascia lata being the most satisfactory portion to work with, as it is easily separated from the underlying tissues. In a few instances the strong abdominal fascia was employed.

The fascia was transplanted in both single and double layers and in one or two instances was twisted.

In each experiment where adhesions were not desired the fascia lata (ilio-tibial band) was placed with the inner or muscle surface exposed. For example, when a flap of fascia was placed in a peritoneal defect, the muscle or smooth side was turned toward the peritoneal cavity, and it was found that dense adhesions were less likely to occur than when the outer side was turned towards the cavity.

In this series, unless otherwise stated, the fascia was transplanted into the same animal from which it was taken.

An attempt was made to place free flaps of fascia on the various tissues, in order to test its vitality and obtain an idea of its possibilities for clinical use.

Experiments.—For convenience I have divided the series into eight groups. To economize space I will only report a few of the typical experiments in each group.

Group I.—Transplantation of Free Fascia into Subcutaneous Tissue on Fat, Muscle, Periosteum, Naked Bone, Cartilage, Tendons and Ligaments.

Experiment 6.—Male, black mongrel; about 9 months old.

Operation.—November 22, 1910. A piece of fascia lata was sutured in the subcutaneous tissue of the chest wall. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

February 23. Distemper. The animal was sacrificed. *Autopsy.*—The fascia was somewhat thickened but otherwise it seemed normal. It was strong and tough.

Histology.[2]—(Microscopic examination.) Showed apparently normal fascia with fibers and nuclei clearly stained. No degeneration.

Experiment 7.—Female, white fox terrier; about 6 months old.

Operation.—November 28, 1910. The sartorius muscle was exposed and a broad band of fascia lata was sutured snugly around it. The wound was closed in the usual manner. No dressing. Condition on leaving the table excellent. *Per primam* healing.

January 16, 1911. Animal sacrificed. *Autopsy.*—The fascia was somewhat thickened but otherwise it seemed normal. The fascia band could be easily stripped from the muscle.

Histology.—(Microscopic examination.) The sections showed normal fascia with no signs of degeneration.

Experiment 8.—Female, tan mongrel; about 6 months old. November 29, 1910. A flap of fascia lata was removed from the thigh and wrapped in moist salt gauze and then placed in the ice box in a sterile jar.

Operation.—December 1, 1910. The fascia which was placed in the ice box 48 hours before was sutured on the ribs, under the muscle. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

January 24, 1911. Animal sacrificed. *Autopsy.*—The fascia was thickened but otherwise it seemed normal. It was movable on the ribs.

Histology.—(Microscopic examination.) The sections showed normal fascia with clearly stained nuclei and fibers.

Experiment 9.—Male, black and white fox terrier; about 2 years old.

Operation.—December 1, 1910. The right femur was exposed and the periosteum was stripped back for about 2 cm. Into this defect a band of fascia lata was sutured around the bone. The wound was closed in the usual manner. No dressing. Condition on leaving the table excellent. *Per primam* healing.

December 27. Death from pneumonia. *Autopsy.*—The band of fascia was somewhat thickened and was intimately blended with the periosteum on either side. The structure of the fascia could be plainly seen.

Histology.—(Microscopic examination.) The sections showed normal fascia with no signs of degeneration.

Experiment 43.—Female, white mongrel; about 2 years old.

Operation.—March 14, 1911. The trachea was exposed and a large flap of fascia was sutured on it. This fascia had been removed from another animal on February 7, 1911, and had been in cold storage since that date. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

April 10. Death from distemper. *Autopsy.*—The fascia was somewhat thickened but otherwise it seemed normal. It was closely adherent along the margins and seemed to blend with the tissues on the surface of the trachea.

Histology.—(Microscopic examination.) The sections showed normal, well-nourished fascia.

Comment.—In this group free fascia flaps were successfully transplanted into the subcutaneous tissue, into fat, on muscle, periosteum, bone, cartilage, tendons and ligaments.

Microscopic examination of the specimens showed that the fascia retained it own structure after transplantation and was apparently healthy and well nourished. This was true

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experimental-clinical articles have appeared. They will be considered fully in another report.

Hohmeier, F.: Experimente über Verschluss von Wunden und Ueberbrückung von Defecten Schleimhauttragender Körpercanäle und -höhlen durch freie auto-plastic. Arch. f. klin. Chir., 1911, p. 345.

König, F.: Neue Wege der plastischen Chirurgie. (Verschluss und Ueberbrückung.) Arch. f. klin. Chir., 1911, XCIV, 326.

Lewis, D. & Davis, C. B.: Experimental Direct Transplantation of Tendon and Fascia. J. Amer. Med. Assoc., 1911, LVII, 540.

[2] I take this opportunity of thanking Dr. C. D. Deming for assistance in the histological examinations.

even after the fascia had been kept in cold storage for thirty-five days and then transplanted into another animal.

The clinical uses suggested by these experiments are of considerable importance, and cover a wide field.

Group II.—Transplantation of Free Fascia into Tendon and Muscle Defects.

Experiment 16.—Male, black mongrel; about 6 months old.

Operation.—December 19, 1910. The right tendo Achillis was exposed and a section about 2.5 cm. long was removed. The stumps were held in position by a strong tension suture, and then a flap of fascia lata was placed in the defect so as to surround the stumps like a tube. This tube was then drawn tight and the ends were securely sutured around the stumps. The tension suture was cut and the dead spaces obliterated. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

Fig. 1.—*Experiment 16.* Fascia to replace tendo Achillis. Operation, December 19, 1910. Specimen removed, March 7, 1911. Comparison of new and normal tendons. The new tendon is thicker than the normal. The + marks the operated leg.

March 7, 1911. Distemper. Sacrificed. The animal had been very active and had no limp. It was imposible to tell which leg had been operated on without close inspection. *Autopsy.*—The replaced tendon was thicker than normal, but seemed strong and satisfactory in every way. (Fig. 1.)

Histology.—(Microscopic examination.) Cross section of the new tendo Achillis showed normal staining fascia which was folded on itself. Surrounding the fascia was connective tissue, which caused the apparent thickening of the new tendon.

Experiment 20.—Male, white fox terrier; about 4 months old.

Operation.—January 3, 1911. The sartorius muscle was exposed and a section about 2.5 cm. long was removed. The muscle ends were held in position and a flap of fascia lata was sutured into the defect surrounding the muscle stumps by a tube of fascia. The dead space was obliterated and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

February 1. Death from pneumonia. Since the healing the animal had been very active and no difference could be detected in the gait. *Autopsy.*—The fascia was firmly united with the muscle ends. (Fig. 2.)

Histology.—(Microscopic examination.) The sections showed fascia with fibers and nuclei clearly stained.

Comment.—This group shows that muscle and tendon defects may be bridged by free flaps of fascia. Muscle defects may be bridged by means of fascia flaps and thus a certain amount of the muscle function saved. The fascia united firmly with the muscle ends and formed a strong symmetrical band between them.

Fig. 2.—*Experiment 18.* Fascia replacing defect in sartorius muscle. Operation, December 27, 1910. Specimen removed, January 14, 1911. The thick muscle ends can be seen, and connecting them is the fascia which has united firmly to them.

The use of fascia flaps to replace tendons is of especial importance and most promising clinically. While it is a well-known fact that free tendon transplantation can be successfully done, it must be borne in mind that it is often difficult to secure either long or short pieces of tendon without doing considerable damage.

There are large amounts of fascia available in the body which can be secured without damage to any other working part. Thus tendons of any desired length might be made from strips of the ilio-tibial band of the fascia lata.

Experimentally the tendons made of folded strips of fascia are not liable to adhere to surrounding tissues. Fascia flaps might also be used to prevent tendons from being caught in scar tissue. The final results after replacing tendons with this material are more satisfactory than with any foreign material or transplantable tissue with which I am familiar.

Group III.—Transplantation of Free Fascia Around Vessels and Nerves.

Experiment 33.—Female, black and yellow mongrel; about 1 year old.

Operation.—February 14, 1911. The right jugular vein was dissected out and a flap of fascia lata was wrapped about it. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

March 3. Death from pneumonia. *Autopsy.*—The fascia was thickened but otherwise seemed normal. It was quite adherent

Fig. 3.—*Experiment 41.* Fascia around vessels and on trachea. Operation, March 14, 1911. Specimen removed, April 11, 1911. On the right carotid can be seen a flap of fascia which was transplanted immediately from the same animal. On the left carotid and trachea are flaps of fascia from another animal which had been in cold storage for 35 days.

to the vessel wall. The lumen of the vessel was not encroached upon.

Histology.—(Microscopic examination.) The sections showed the structure of the vessel to be normal. It was surrounded by a band of fascia which was apparently well nourished and showed no signs of degeneration.

Experiment 41.—Female, yellow and white mongrel; about 1 year old.

Operation.—March 14, 1911. Both common carotid arteries were exposed. Around the right carotid a piece of fascia lata was sutured, which had just been removed from the right thigh. Around the left carotid was sutured a piece of fascia which had been removed from another animal on February 7, 1911, and had been in cold storage since that date. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

April 10. Death from pneumonia. *Autopsy.*—The fascia on both carotids was thickened, but otherwise seemed normal. The appearance of the two specimens was the same. The fascia was quite adherent to the vessels but could be stripped off. The lumen of the vessels was not encroached upon. (Fig. 3.)

Histology.—(Microscopic examination.) The sections showed apparently normal fascia in both instances. No signs of degeneration.

Experiment 44.—Male, black and white fox terrier; about 1 year old.

Operation.—March 21, 1911. The right sciatic nerve was exposed and a flap of fascia lata was sutured around it. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing. Gait unaffected.

April 20. Distemper, animal sacrificed. *Autopsy.*—The fascia was thickened but otherwise seemed normal. It could be moved on the nerve to a slight degree. There was no constriction of the caliber of the nerve.

Histology.—(Microscopic examination.) The sections showed a normal nerve surrounded by well-nourished, apparently normal, fascia.

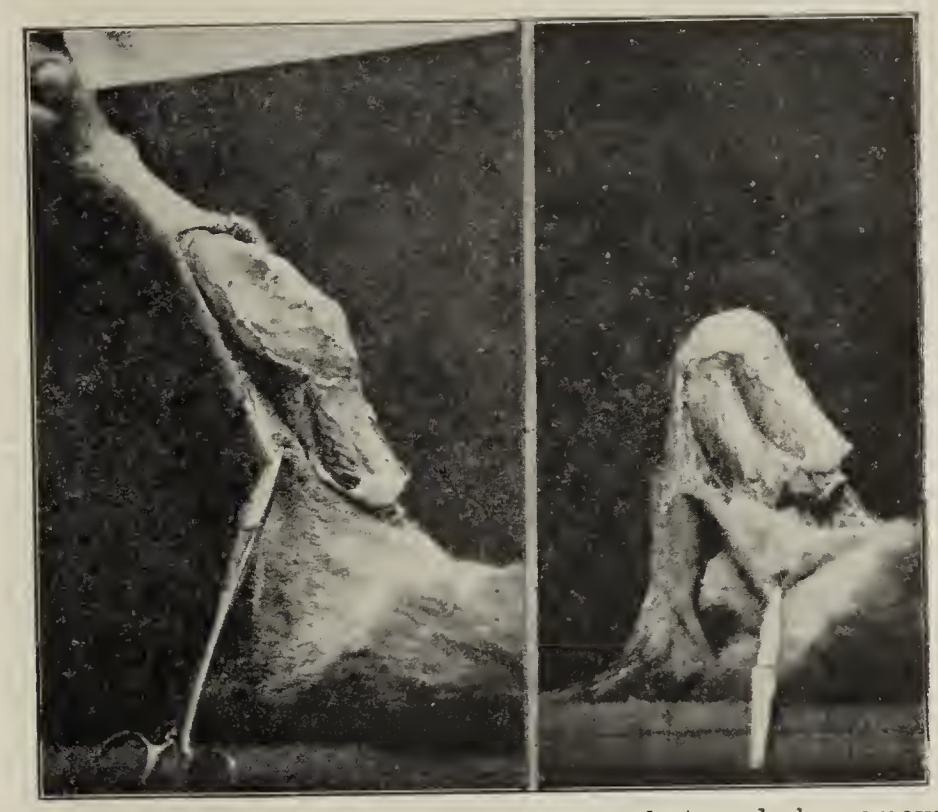


Fig. 4.—*Experiment 22.* Fascia filling defect made by removal of patella. Operation, January 9, 1911. Specimen removed, February 2, 1911. Note the amount of extension and flexion possible. The fascia can be seen firmly healed to the joint capsule.

Comment.—This group shows that free flaps of fascia may be successfully transplanted around arteries, veins and nerves, without in any way interfering with the lumen of the vessels, or compressing the nerves.

Clinically, fascia flaps might be of use in protecting suture lines in vessel surgery and in reenforcing weakened areas in vessel walls. The site of nerve plastic operations might be surrounded and protected by such flaps. It might also be of use in protecting a nerve after it was freed from callus or scar tissue.

Group IV.—Transplantation of Free Fascia into Joints and for Suturing Fractured Bones.

Experiment 22.—Female, yellow mongrel; about 6 months old.

Operation.—January 9, 1911. The left patella was removed and a piece of fascia lata was substituted for it. The fascia

was folded on itself so that its inner smooth surface was next to the joint, and also under the skin. It was sutured to the capsule and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

February 2. Pneumonia, animal sacrificed. The joint was freely movable and as far as could be seen had been as serviceable as the normal knee. (Fig. 4.) *Autopsy.*—The fascia was easily separated from the skin. It had adhered firmly to the joint capsule. On opening the joint the surface of the fascia was perfectly smooth. There were no adhesions. The fascia was slightly thickened.

Histology.—(Microscopic examination.) The sections showed a double thickness of apparently normal fascia. The staining of fibers and nuclei was well marked. (Fig. 5.)

(a)

(b)

(c)

FIG. 6.—*Experiment 29.* Fascia into joint after removal of the cartilage. Operation, February 6, 1911. Specimen removed, February 28, 1911. (a) Leg extended, compared with normal. (b) Leg flexed, compared with normal. (c) Inside of joint. The + marks the operated joint.

EXPERIMENT 29.—Female, white fox terrier; about 8 months old.

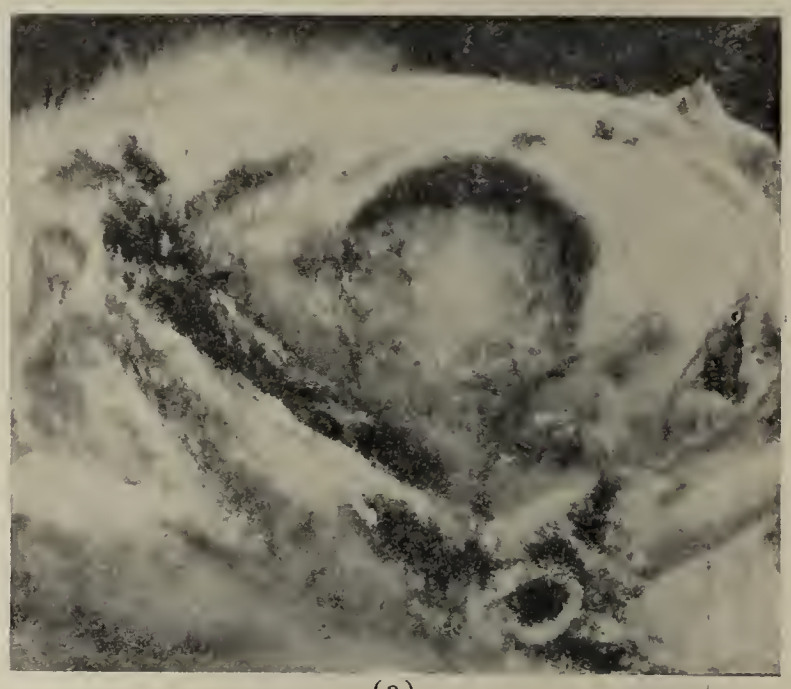
Operation.—February 6, 1911. The right knee-joint was opened and the entire articular cartilage was removed as thoroughly as possible. Then a piece of fascia lata was inserted and sutured over the denuded portion of the femur and well up under the patella. The joint was closed. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

February 27. Death from pneumonia. Since the dressing was removed the animal has been using the operated knee-joint without apparent discomfort. *Autopsy.*—The joint was movable. The fascia was slightly thickened. It was adherent to the denuded end of the femur, but to no other portion of the joint. Its structure was well preserved. (Fig. 6.)

Histology.—(Microscopic examination.) The sections showed normal staining, well-nourished fascia. No signs of degeneration or absorption.

EXPERIMENT 31.—Male, yellow and white mongrel; about 6 months old.

Operation.—February 13, 1911. The right tibia was exposed and the periosteum stripped back. The bone was sawed through and then two strips of fascia lata were passed through drill holes and tied. The tied ends were made additionally secure by sutures. The wound was closed and a small drain was inserted in the lower angle. Dry dressing, crinolin and splint.



(a)

(b)

FIG. 7.—*Experiment 38.* Fascia into skull and dura defect. Operation, March 6, 1911. Specimen removed, April 20, 1911. (a) Bone defect from outside with fascia adherent to bone edges. (b) From within the outline of the bone defect can be seen. The fascia is closely adherent to the dura which extends beyond it. The fascia is smooth except for one small adhesion in the center.

Condition on leaving the table excellent. The stitches were removed on the fifth day. The wound was apparently nicely healed. It was practically impossible to immobilize the broken bone.

February 23. Distemper, animal sacrificed. *Autopsy.*—On removing the dressing the wound was found badly infected. In spite of the infection the strength of the fascia was apparently but little affected and the strips were still holding the ends of the bone together. This specimen was accidentally lost.

Comment.—This group is also interesting. Free flaps of fascia were successfully transplanted into joints and also to take the place of patellæ which had been removed. Both of these procedures are suggestive clinically.

Bones were fractured and the fragments sutured with strips of fascia. The result of these last experiments were unsatisfactory on account of the difficulty in immobilizing the fragments. However, the use of fascia strips in the open treatment of fractures in human beings may be of great use clinically, as immobilization can be secured.

The fascia does not act as a foreign body and has strength enough to stand any reasonable strain put upon it.

Group V.—Transplantation of Free Fascia into Defects in the Skull and Dura, also into Tracheal Defects.

Experiment 38.—Male, yellow mongrel; about 1 year old.

Operation.—March 6, 1911. The left temporal muscle with the underlying periosteum was turned back and a ¾-inch button of bone was removed. The dura under this area was excised and a flap of fascia lata was tucked under the bone edges. The smooth muscle side of the fascia was placed next to the brain. The temporal muscle was replaced and sutured, and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

April 20. Distemper, animal sacrificed. *Autopsy.*—There was one small adhesion of the cortex to the central portion of the fascia. The edges of the fascia and dura were intimately blended. The structure of the fascia could be plainly seen. The fascia was tightly stretched across the bone defect and was firm and did not bulge on pressure. (Fig. 7.)

Histology.—(Microscopic examination.) The sections showed normal staining, apparently well-nourished fascia.

Experiment 62.—Female, black mongrel; about 1 year old.

Operation.—June 12, 1911. The trachea was exposed and an area 8 mm. square was excised. Over this defect was sutured securely a flap of fascia lata. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing. There was no cough or any respiratory symptom following the operation.

July 3. Animal sacrificed. *Autopsy.*—The fascia was somewhat thickened and firmly adherent to the surface of the trachea. There had been no leakage whatever. On opening the trachea from behind, the defect was made out as a very shallow depression and the fascia seemed to be entirely covered with mucous membrane, which had grown over it. (Fig. 8.)

Histology.—(Microscopic examination.) The sections showed the defect filled by normal staining, apparently well-nourished fascia. Over this fascia, as a base, the mucous membrane had grown, completely covering it. (Fig. 9.)

Comment.—This group shows that flaps of fascia inserted in skull defects between the dura and bone edges will heal and give a strong membrane which will resist considerable pressure from within and without. When the dura is removed in addition to the bone the fascia flap tucked under the bone edges will unite with the dura and also become tightly adherent to the bone edges.

There was in each instance a single fine adhesion of the cortex to the center of the fascia flap.

Fascia flaps might be used clinically in repairing skull defects and as an aid in the closing of a spina bifida.

This group also shows that free flaps of fascia may be successfully used to cover prepared defects in the trachea, without subsequent infection, and that the mucous membrane grows across the fascia covering the defect.

It might be of use, clinically, in closing old tracheotomy wounds, where there has been considerable destruction of cartilage, and also in reenforcing sutures of the trachea.

(a) (b)

(c)

Fig. 8.—*Experiment 62.* Fascia over defect in trachea. Operation, June 12, 1911. Specimen removed, July 3, 1911. (a) Shows normal trachea with opening in it the size of that covered by the fascia. (b) The fascia healed over a similar defect. (c) The same specimen from within, showing a slight depression which marks the defect. The mucous membrane has grown completely over the fascia.

Group VI.—Transplantation of Free Fascia into Prepared Defects in the Abdominal Wall.

Experiment 17.—Male, white and black fox terrier; about 1 year old.

Operation.—December 22, 1910. All the tissues of the abdominal wall between the skin and the peritoneum were excised from an area about 4 x 7 cm. Into this defect a flap of fascia

lata 3 x 6 cm. was sutured. The skin was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

June 27, 1911. Animal sacrificed. *Autopsy.*—There was no hernia or bulging of the abdominal wall at the site of operation. From within there was no depression in the parietal peritoneum. On holding the specimen to the light the outline of the inserted fascia could be readily seen. The fascia itself was slightly thickened but normal in every way and was strong and tough.

Histology.—(Microscopic examination.) The sections showed normal staining fascia with no signs of degeneration.

Experiment 19.—Male, brown and black mongrel; about 1 year old.

Operation.—December 29, 1910. The peritoneum was exposed and an area 4 x 2 cm. was excised. Into this defect a piece of fascia lata was sutured. The wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

February 7, 1911. Animal sacrificed. *Autopsy.*—The fascia edges had blended with the peritoneum. It was thickened but otherwise seemed normal. There was a small omental adhesion.

Histology.—(Microscopic examination.) The sections showed normal, well nourished fascia.

Experiment 46.—Male, yellow and white mongrel; about 1 year old.

Operation.—March 23, 1911. A section of the abdominal wall 3 x 7 cm., including everything except the skin, was excised. Into the peritoneal defect was sutured a flap of fascia lata from one thigh, and into the muscle defect a flap from the other thigh. The skin was closed in the usual manner. Dry dressing. Condition on leaving the table excellent.

The animal developed distemper three days after the operation and on the fifth day the skin wound broke down. There was no hernia as the fascia held firmly.

April 6. Death from distemper. *Autopsy.*—There was a crater like ulcer whose base was made up of fascia on which granulations could be seen both at the edges and scattered over the surface. There was no hernia whatever and the fascia seemed to be strong and intact. On opening the abdominal cavity there was free pus and this was also found in the pleural cavity. The omentum was adherent over a small part of the fascia. The fascia was incorporated with the peritoneum and had healed firmly in position.

Histology.—(Microscopic examination.) The sections showed infiltration with leucocytes, and marked signs of infection. The fascia was apparently in good condition with clearly stained fibers and nuclei. There was definite granulation tissue growing from the ulcer edges out on the fascia.

Comment.—This group shows that free flaps of fascia may be sutured into peritoneal and muscle fascia defects in the abdominal wall, and that it will incorporate itself with the surrounding peritoneum and muscle edges. A small omental adhesion was present on examination of the specimen in each instance, but in no case was there adhesion of the gut or any other abdominal organ to the fascia.

When a hernia was produced by the removal of a portion of the abdominal wall, except the skin, it was readily cured several weeks later by the transplantation of fascia flaps.

These experiments suggest the use of fascia flaps in the cure of large hernia where the muscle is atrophied, and for strengthening any weakened area in the abdominal or chest wall. The facility with which the fascia unites with the peritoneum suggests its further use in pleural and pericardial defects.

Group VII.—Transplantation of Free Fascia onto Stomach, Intestine and Bladder.

Experiment 23.—Female, brown and black mongrel; about 1 year old.

Operation.—January 10, 1911. The bladder was brought up through a mid-line incision and a flap of fascia lata was sewed to it with a continuous suture. The bladder was dropped back and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

July 27. Animal sacrificed. *Autopsy.*—There were omental adhesions to the fascia. The peritoneum on the surface of the bladder was somewhat puckered under and immediately around the fascia edges. The fascia itself was thickened but otherwise seemed normal.

Histology.—(Microscopic examination.) Normal staining fascia found. The peritoneal covering of the bladder could not be differentiated.

Experiment 24.—Female, yellow mongrel; about 6 months old.

Operation.—January 16, 1911. The stomach was exposed and an incision 3.5 cm. long was made in it, down through the mucosa. This was then closed with the Cushing continuous stitch and over the suture line was placed and sutured a flap of fascia lata. The stomach was dropped back and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

January 27. Distemper, animal sacrificed. *Autopsy.*—The fascia was thickened but otherwise seemed normal. It was closely adherent to the stomach wall. There were a few omental adhesions to the fascia but these could be easily separated.

Histology.—(Microscopic examination.) The sections showed the line of suture. Above this was the layer of fascia which was apparently normal and well nourished.

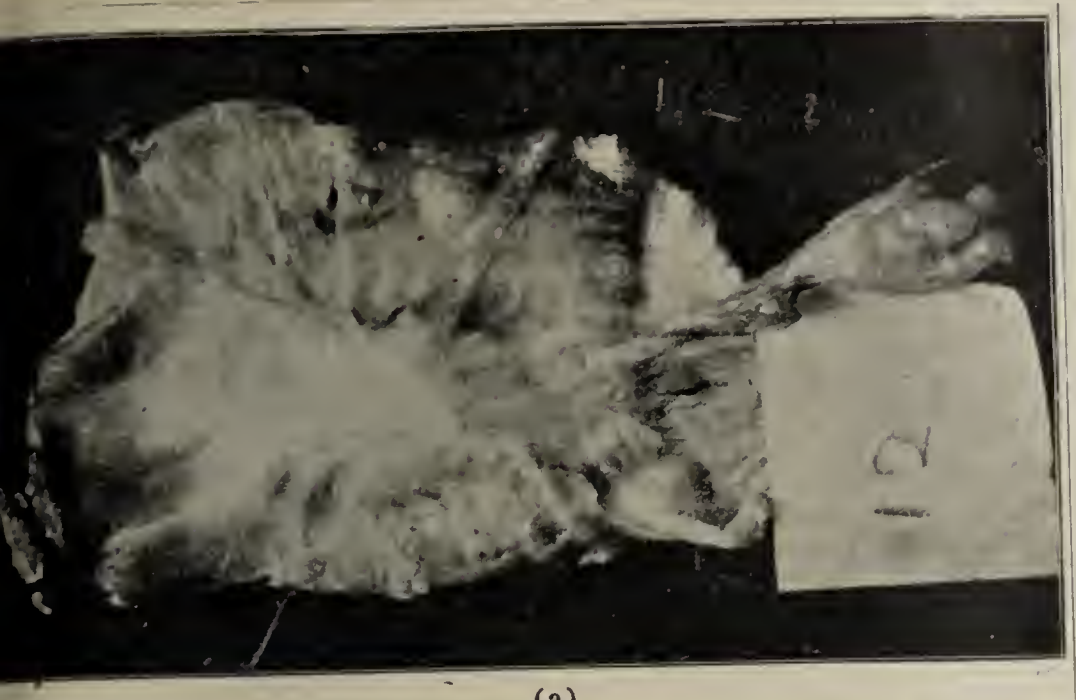
Experiment 61.—Male, black and white fox terrier; about 1 year old.

Operation.—June 5, 1911. A loop of gut was brought up through an abdominal incision and a purse string suture was placed opposite the mesentery. When the suture was drawn tight and tied the portion within the suture projected outward. The tip of the projection was cut off exposing the lumen of the bowel. Over this area a flap of fascia lata was sutured snugly and the gut was dropped back. The wound was closed in the usual manner. Dry dressing. *Per primam* healing.

July 3. Animal sacrificed. *Autopsy.*—The omentum was adherent to the fascia but this was easily separated. The fascia was somewhat thickened but otherwise seemed normal. It was closely adherent and seemed incorporated with the peritoneum of the bowel. There was a definite puckering of the wall of the gut around and under the fascia. There had been no leakage From within a small depression in the mucous membrane corresponding to the pucker made by the purse string could be seen.

Histology.—(Microscopic examination.) The sections showed normal staining, well-nourished fascia. There was marked infiltration of the tissue beneath the fascia with polynuclear leukocytes. There was a great mass of these cells in the area corresponding to the made defect. On the surface of the fascia was the remains of the adherent omentum.

Comment.—In this group free fascia flaps were successfully transplanted onto the stomach, the intestine and the bladder. The fascia seemed to incorporate itself with the peritoneum (Fig. 10).



(a)

(b)

(c)

Fig. 10.—*Experiment 19.* (a) Fascia in peritoneal defect. Operation, December 29, 1910. Specimen removed, February 7, 1911. *Experiment 23.* (b) Fascia on bladder. Operation, January 10, 1911. Specimen removed, June 27, 1911. *Experiment 61.* (c) Fascia over defect in intestine. Operation, January 5, 1911. Specimen removed, July 3, 1911.

In all of these the fascia was thickened. It was incorporated with the peritoneum and there was a puckering of the peritoneum at the margin of the fascia. There was adherent omentum in each case. A small tag can be seen in (a).

Clinically fascia might be used to strengthen suture lines and weakened areas due to ulceration. It might also be of use in closing fistulæ of one sort or another.

Group VIII.—Transplantation of Free Fascia on Liver, Kidney and Spleen.

Experiment 36.—Female, brindle mongrel; about 18 months old.

Operation.—February 21, 1911. Through a lumbar incision the left kidney was exposed and after the capsule was stripped back an abrasion of the surface was made and a flap of fascia lata was sutured over it. The hemorrhage ceased promptly. The kidney was dropped back and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

March 7. Distemper, animal sacrificed. *Autopsy.*—The skin wound which had apparently healed became infected after the development of the distemper. The fascia was adherent to the surrounding tissues. It was not much thickened and seemed normal. It was tightly adherent to the kidney at the edges, but could be stripped up more easily in the center of the flap.

Histology.—(Microscopic examination.) The sections showed normal fascia closely adherent to the parenchyma.

Experiment 52.—Male, black mongrel; about 3 months old.

Operation.—May 8, 1911. Through a high mid-line incision a lobe of the liver was exposed. The end of the lobe was cut off with scissors leaving a bleeding area 3 cm. x 6 mm. Over this surface was placed a flap of fascia lata and the bleeding was markedly checked. The fascia covered the end like a shallow cap, and was held in position by mattress sutures passing through the liver substance and through both sides of the fascia. These sutures were drawn as tight as desired and did not cut through the liver substance. The liver was dropped back and the wound was closed in the usual manner. Condition on leaving the table excellent. *Per primam* healing.

June 6. Death from pneumonia. *Autopsy.*—There was adhesion of the omentum to the fascia. When this was stripped off the fascia was seen covering the denuded area like a cap. It was slightly thickened but otherwise seemed normal.

Histology.—(Microscopic examination.) The sections showed normal staining, well-nourished fascia surrounding an area of liver substance. It was adherent to a considerable extent.

Experiment 60.—Black and white fox terrier; about 1 year old.

Operation.—June 5, 1911. The spleen was brought up through a left rectus incision, the edge was trimmed with scissors, and a flap of fascia was sutured over the denuded area so as to bind it. The fascia was held with mattress sutures which passed through the spleen and both edges of the fascia. There was considerable hemorrhage until the fascia was applied and the sutures tied. The spleen was dropped back and the wound was closed in the usual manner. Dry dressing. Condition on leaving the table excellent. *Per primam* healing.

July 3. Animal sacrificed. *Autopsy.*—The fascia was thickened and securely bound the edge of the spleen. It seemed well nourished and it could be separated from the spleen quite easily.

Histology.—(Microscopic examination.) Sections showed normal staining fascia surrounding spleen tissue.

Comment.—In this group free flaps of fascia were successfully transplanted on the liver, kidney and spleen. It suggests that the fascia flaps might be used to support sutures in these organs, and also to bind raw post-operative surfaces (Fig. 11).

It is to be noted that the fascia when applied to a bleed-

ing surface seemed to have a definite hemostatic effect which is comparable to the hemostatic action of bits of muscle, spoken of by Cushing.

The kidney might be suspended to the ribs or muscles in a sling of free fascia. These results are very promising.

(a)

(b)

FIG. 11.—*Experiment 25.* (a) Fascia on a lobe of the liver. Operation, January 17, 1911. Specimen removed, January 26, 1911. The fascia was thickened but was adherent to the liver surface over most of its extent. *Experiment 36.* (b) Fascia on kidney cortex. Operation, February 21, 1911. Specimen removed, March 7, 1911. The fascia is closely adherent to the kidney substance and blends with the capsule.

In both of these specimens, as in all the others, the fascia was well nourished.

Remarks.—In none of the animals have I noted a muscle hernia after the fascia was removed, but should it occur the hernia could be repaired without difficulty. There is apparently no untoward effect after removal of the fascia lata as far as the use of the limb is concerned.

In every instance the fascia retained its own structure and seemed well nourished. After removal from its bed it was as tough and strong as when first transplanted.

The great strength of the fascia, and, in addition, its thinness and flexibility are to be noted. It can be sutured into a defect under considerable tension, and the sutures will hold securely even when inserted close to the edges or ends of the flap.

The great supply of this material and the ease with which it can be obtained are important points.

There is some difference in the measurements of flaps of fascia before and after removal. For example: A marked out flap of fascia lata measured 4.5 x 2.5 cm. before removal, and after removal it measured 3.3 x 2 cm. Another flap measured before removal 4.5 x 2.2 cm. and after removal 4 x 1.75 cm.

In several experiments fascia was drawn taut and sutured around firm rubber tubes 0.8 to 1 cm. in diameter, and then inserted in the subcutaneous tissue. These specimens were removed after forty-nine and fifty-four days. The structure of the fascia could easily be seen. Microscopic examination showed normal staining fascia with no signs of degeneration.

This is interesting as it shows that fascia will receive sufficient nourishment if only one surface is exposed to living tissue.

The type of so-called distemper prevalent in the laboratory this winter appeared to have some effect on the healing of the wounds and a number of them became infected. This did not seem due to a break in technic, as other animals operated on the same morning (before and after these animals), with identical technic, and not developing the distemper, did not break down.

In several animals whose stitches had been removed after per primam healing the skin wound subsequently broke down after the development of distemper.

In the instances where there was infection the transplanted fascia seemed particularly resistant to it, and retained its structure after the breakdown of the surrounding tissues.

Where there was tension on the fascia there was comparatively little thickening, but wherever the fascia was simply laid on a tissue there was always thickening, and unless it was held flat with sutures it had a tendency to bunch or roll up.

Once or twice the fascia flap was accidentally allowed to partially dry out before it was transplanted, but, in spite of this, it was moistened with salt solution and transplanted. The results were excellent and the fascia was nourished and grew in its new position.

The question naturally arose as to the necessity of transplanting the fascia immediately, and also whether fascia from one animal could be successfully transplanted into another.

Experimentally, both of these questions have been answered satisfactorily.

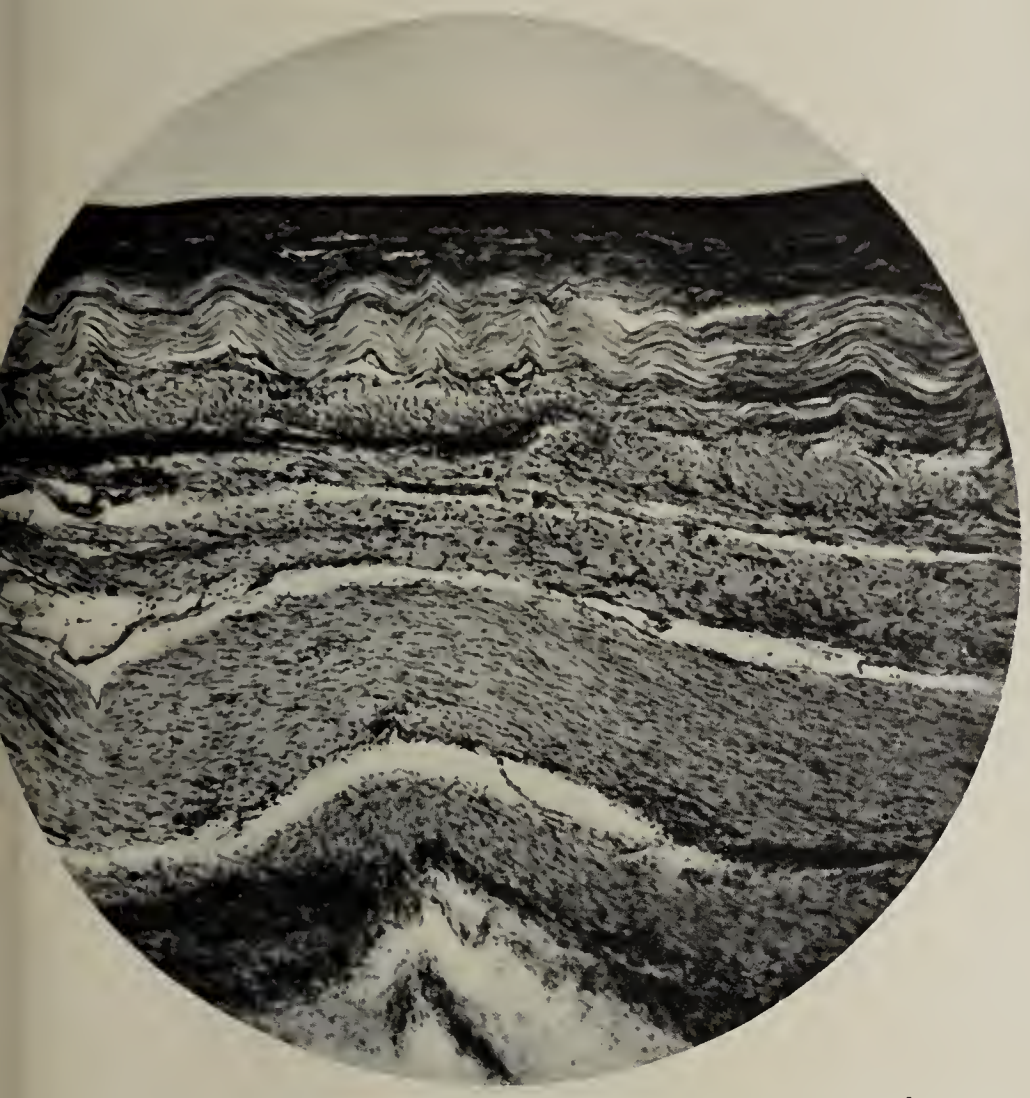


FIG. 5.—(Microphotograph, Zeiss. Obj. AA. Oc. 3.) Two layers of fascia filling defect left by removal of patella. Section cut parallel to fascia bundles. The smooth dark staining layer at the bottom of the plate is the portion toward the joint cavity.

FIG. 12.—(Microphotograph, Zeiss. Obj. AA. Oc. 3.) Fascia preserved in cold storage wrapped in moist salt gauze for 35 days and then transplanted on the surface of a trachea. Operation, March 14, 1911. Specimen removed, April 10, 1911. The section is cut across the fascia bundles. The fascia is normal in appearance and stains well.

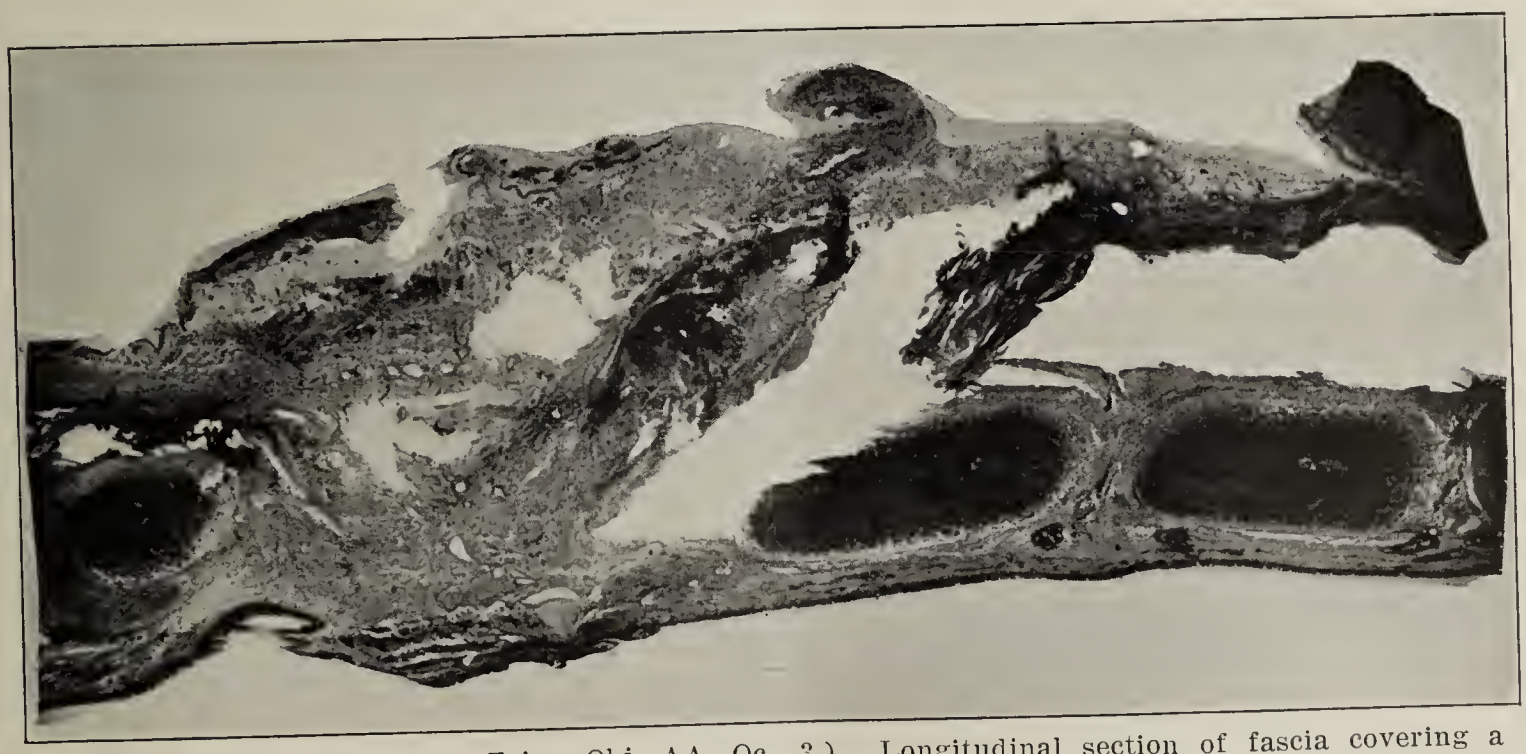


FIG. 9.—(Microphotograph, Zeiss. Obj. AA. Oc. 3.) Longitudinal section of fascia covering a tracheal defect. The defect can be seen between the tracheal rings. On the right of the plate the fascia has become accidentally separated from the surface of the trachea during the preparation of the section. The mucous membrane can be seen covering the fascia.

Fascia was successfully transplanted into the same and other animals after being kept in an ordinary ice chest at 38° C. for as long as seven days; in cold storage at 32° C. wrapped in gauze moistened with salt solution for thirty-five days, and in cold storage at 32° C. in normal salt solution for fifty-six days. (Fig. 12.)

I am sure that the number of days given here does not show the greatest time that fascia may be preserved by the methods spoken of, but I mention the periods as a suggestion that suitable fascia might be preserved until needed for clinical use.

Fascia kept in salt solution appeared edematous when first removed from the solution, but the edema disappeared when the tissue was pressed with dry gauze. The edema was entirely in the superficial connective tissue which had not been removed. The fascia kept in moist salt gauze, on the other hand, was normal in appearance.

When fascia was sutured to the surface of the stomach, intestine or bladder within a few days there was the appearance of puckering or drawing up of the surface under the fascia and at its edges, somewhat similar to the effect of ordinary collodion on the skin. On this area, from within the organ, this puckering was not to be found and the lumen was in no way encroached upon.

The hemostatic action of free fascia flaps is noteworthy.

Conclusions.—The foregoing experiments give an idea of the great possibilities of transplanting free flaps of fascia and many suggestions for the clinical use of this substance may be drawn from them.

I feel convinced that many of the difficult situations arising during operations for the repair of weakened and defective tissues or for the control of bleeding surfaces will be simplified by the use of free fascia flaps and shall report the results of its use in such cases, with a consideration of the literature, in a subsequent paper.

NOTES ON NEW BOOKS.

Progressive Medicine. Edited by Hobart Amory Hare, M. D., etc., assisted by Leighton F. Appleman, M. D., etc. Vol. II. June, 1911. (*Lea & Febiger: Philadelphia and New York, 1911.*)

Coley contributes the chapter on "Hernia," Gerster that on "Surgery of the Abdomen, Exclusive of Hernia," Clark that on "Gynecology," Stengel that on "Diseases of the Blood, Diathetic and Metabolic Diseases; Diseases of the Thyroid Gland, Nutrition, and the Lymphatic System"; and Jackson that on "Ophthalmology." It is interesting in looking over these quarterly volumes to consider how much or how little of all the literature is of permanent value; and whether an annual volume of limited size might not be of greater value; but *Progressive Medicine* is well edited and satisfies a natural demand of the profession.

A Textbook of Nervous Diseases. By William Aldred Turner, M. D. (Edin.), and Thomas Grainger Stewart, M. B. (Edin.) Price, $6. (*Philadelphia: P. Blakiston's Sons & Co., 1910.*)

This book contains 607 pages, including the index. It is well printed, well illustrated, and well bound, opening well, but the unusual purple color of the binding is somewhat startling at first. The work is divided into nineteen parts, instead of chapters, as follows: Anatomy and Physiology, Examination of the Nervous System in a Case of Nervous Disease, The Special Senses, The Cranial Nerves, The Peripheral Nervous System, The Diseases of the Brain, Diseases of the Membranes, Diseases of the Spinal Cord, General Diseases of the Nervous System, Vasomotor and Trophic Diseases, Familial Diseases, Diseases Characterised by Disorders of Muscular Function, Diseases of Obscure Origin Characterised Chiefly by Disorders of Motion, Migraine and Periodic Headache, Hysteria, Neurasthenia, Psychasthenia, Epilepsy, and The Tics. It will be generally agreed that the above arrangement is an excellent one and examination of the work proves it. The authors have so often shown their ability to do excellent work in the past that it goes without saying that they have kept up their reputation in this more ambitious undertaking. We find but little to criticise and that of a trivial nature. Here and there it would perhaps have been better to have enlarged somewhat on certain statements or to have gone more into details but of a necessity brevity would have been sacrificed. One statement we feel should be modified and this appears in two forms, one on page 402, in speaking of the cerebro-spinal fluid, of progressive general paralysis: "The lymphocytes are greatly increased in number—to 150 or 200 or more [per] c. mm. of fluid—and the Wasserman reaction is present in 90 per cent or more of the cases (Mott)." And again on page 553 in discussing the diagnosis of neurasthenia from the neurasthenic type of early paralytic dementia it states as follows: "This occurs chiefly in adult males who have had syphilis. Such cases may, or may not, present physical signs of organic disease, such as loss of the tendon jerks, or reflex pupillary immobility. If these signs are found in association with neurasthenic symptoms, the onset of paralytic dementia may almost with certainty be diagnosed. The failure to obtain these signs of organic disease does not necessarily exclude the onset of paresis; therefore in those cases a lumbar puncture ought to be done and a cytological examination made of the cerebro-spinal fluid. If, on examination of the centrifuged deposit, the lymphocyte count shows 150 to 200 or more lymphocytes, the diagnosis of general paralysis may be made with complete assurance. Although an increase of the lymphocytes is present in most cases of cerebrospinal syphilis, yet the count is rarely so high as in the parasyphilitic diseases." The first statement is not entirely clear as the word *per* is evidently omitted between "more" and "c. mm.," but in regard to both of them we believe that the number is entirely too high, that with such a high count other organic symptoms will undoubtedly be present, and that no competent observer would be willing to make a diagnosis of paresis on a high lymphocyte count alone, no matter how high it might be.

American Practice of Surgery. Editors: Joseph D. Bryant, M. D., LL. D. Albert H. Buck, M. D., vol. VIII. Profusely illustrated. (*New York: William Wood and Co., 1911.*)

With this volume this stupendous system of nearly 9000 pages comes to an end. Both editors and publishers can feel well satisfied with the work, which covers the entire field of surgery as completely, or even more so, than any other system in English. Those who use it will be able to find what they want in it, except that the index is very incomplete, which is a serious defect in such a work. This volume includes chapters on Introthoracic Surgery, Surgery of the Spleen, Surgical Diseases and Wounds

of the Kidneys and Ureters, Surgery of the Pancreas, Surgery of the Liver, Gall-Bladder, and Biliary Passages, Surgical Diseases, Wounds and Malformations of the Urinary Bladder and the Prostate, Surgery of the Ovaries and Fallopian Tubes, Surgery of the Uterus and its Ligaments, Extra-Uterine Pregnancy, and the Caesarian Section and its Substitutes. There are additional sections on The Law in its Relation to the Practice of Surgery, and Administrative Surgical Work, the latter including surgical needs of hospitals, and military, naval and railroad surgery. There is finally an Appendix with a chapter on the Relation of Blood-Pressure to Surgery, and a General Index.

Handbook of Treatment for Diseases of the Eye (Ophthalmic Therapeutics). By Dr. Curt Adam, Berlin. With a preface by Prof. von Michael, Berlin. Translated from the second German edition (1910) by William George Sym, M. D., etc., and E. M. Lithgow, M. B., etc. Illustrated. Price, $2.50. (*New York: Rebman Company, 1911.*)

This little book is devoted to the *treatment* of the diseases of the eye. While the propriety of separating the treatment from the description of the diseases may be questioned, yet it is sometimes very convenient, and it is possible some may like this book very much.

The treatment advocated for the various eye diseases is usually good, and will be found to give good results. The book states very definitely how to treat the various eye diseases, and if the instructions were even blindly followed the results would in almost every case be good and we suppose this means the book will be of value to some readers whose personal experience in such matters is small and who must necessarily follow some formal and definite plan in treating each disease. To all such readers we can commend this book as being about the best and safest of its class.

The Principles and Practice of Bandaging. By Gwilym G. Davis, M. D., etc. Third Edition, Revised. Illustrated. Price, $1. (*Philadelphia: P. Blakiston's Son & Co., 1911.*)

This work, which originally appeared in 1891, has been largely rewritten and the illustrations have been redrawn, so that it is practically a new book. As it exists to-day it is a first-rate guide for beginners as the author intends it to be. The drawings and text are both clear, so that a student should have little difficulty in mastering these principles. The author has divided his work into three parts: The Roller Bandages, The Tailed Bandages or Slings, and the Handkerchief Bandages. This arrangement with an abundance of illustrations makes it easy to acquire the practice of bandaging. The compactness and general excellence of this small manual will make it welcome to students.

Fractures and Their Treatment. By J. Hogarth Pringle, M. B. (Ed.), F. R. C. S. (Eng.), Glasgow. Price, $5.50. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

This book deals first with the general facts in relation to fractures. The usual causes, mechanisms, classification, and general diagnostic signs are discussed in the earlier chapters. Following this is a consideration of the process of repair, and of associated lesions of soft parts and joints. Fractures of particular bones are then described, with the methods of treatment, the anatomical sequence of the skeleton being pursued. The final chapter is devoted to the relation of fractures to the Workmen's Compensation Acts of England. At the end of the book are presented several tables, compiled from various German authorities, indicating the amount of depreciation in working efficiency after certain injuries. The book is well illustrated, and contains a good bibliography, the references to special lesions being grouped together. The literary style of the work shows the usual clearness and purity of British authors. The content of the subject-matter is far from being complete, the handling of most of the particular fractures being limited to a statement of general and well-known facts.

One wonders why such a book was written. There seems no reason for this expenditure of time and labor on a subject already so fully and frequently treated, in every form from text-book articles to special volumes, unless there be some new light to shed of importance enough to justify the task. Such illumination, if present, escaped the reviewer. The book has no especial fault except the deadly one of being commonplace and unnecessary. The writer must have sensed the probability of such criticism. In the preface he states that the X-ray and Workmen's Compensation Laws have made of fractures a comparatively new subject, and further says that he was induced to write the book because no special work on the subject has been published in England for a very considerable time. The last reason does not exist in this country, and one feels if the legal aspect of fractures was a prime motive in the construction of the book, that this phase of the subject has been given a most disproportionately small amount of attention. H. B. Stone.

Medical Guide and Monograph Series. Golden Rules of Pediatrics. By John Zahersky, M. D., etc. With an Introduction by C. W. Saunders, M. D. Price, $2.50. (*St. Louis: C. V. Mosby Company, 1911.*)

Although there is nothing on the title page to indicate that this book has appeared before, the author has written a brief "Preface to the Second Edition," which proves that his rules have been welcome to certain members of the profession. The book has been carefully prepared and contains precepts which are serviceable to the student. One might apply, however, the aphorism to "Golden Rules" of this and other branches of science "that all is not gold that glistens." The success of such works is rather a sad reflection on the mental attitude of the doctor who finds them useful. If he knows his science as he should do he will not need them; and unless he knows his science "Golden Rules" are but a snare and delusion.

A Monograph of the Anopheline Mosquitoes of India. By S. P. James, M. D., etc., and W. Glen Leston, M. D., etc. Second Edition. Rewritten and enlarged. (*Calcutta: Thacker, Spink & Co., 1911.*)

Although this treatise is intended mainly for workers in India; yet there is so much valuable information in it in regard to mosquitoes, that all students interested in the transmission of contagious diseases, especially yellow fever and malaria, will prize it highly. Its most beautiful and copious illustrations are of immeasurable help in appreciating the differences between the genera. The book is divided into two parts. Part I contains three chapters: 1, A general account of mosquitoes; 2, The collecting, mounting and examination of anopheline mosquitoes and their larvæ; 3, The classification and identification of Indian anophelines. Part II contains the description of thirteen genera. Drs. James and Liston are to be most warmly congratulated on their admirable piece of work.

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THE MEDICAL PAINTINGS OF VELASQUEZ.*

By John W. Churchman, M. D.,

Late Resident Surgeon, The Johns Hopkins Hospital.

There is nothing whatever to show that Velasquez felt any particular interest in the tasks of science or in its achievements. He certainly exhibited no feeling for medicine as a profession, or as one of the humanities. The approach of art to science has often been more obvious. Other men, like Leonardo, have made important contributions to each. Not a few—like Keats and Sainte-Beuve—have known, by desertion of the one for the other, the problems and interests of both. Yet Velasquez' mind was of the type which enjoys the dispassionate observation of facts; and in this sense his point of view was at least a new one in art. Vision meant for him, not what it had meant for his predecessors; it meant simply one of the five senses keenly developed and used without fear or favor. Such sympathy with the method of science, despite any indifference to its content, it is not farfetched to describe as intellectual kinship. In this man, art and science drew near; and the gap between them was further narrowed by the fact that the actual phenomena which fell in Velasquez' way chanced to be the ones with which medicine is herself concerned.

Strange as Velasquez' fascination by oddness and deformity of mind and body were, he was by no means unique in his choice of material which happens to have a medical interest. He was, indeed, quite unique in the extent to which his choice was of this character; but the field of medicine he shares with many other painters. There was Jan Steen, for example, in the Netherlands. Yet sunlight and shadow could hardly present a sharper contrast than did these two men; nor could bar-room, where the one idled away his days, and king's-court, where the other lived out his career. In almost every detail and circumstance of outward life and mental outlook what the one man was the other was not. The Dutchman brought to medical life the methods of pictorial art; his interest in medicine was casual and anecdotal. Velasquez was interested neither in episodes nor in events. He apprehended and constantly maintained the purely objective attitude.

The pictures of Velasquez which possess unusual medical interest, belong to the Dwarf and Jester Group.[1] With three exceptions, they were painted in the last ten years of his life and represent, therefore, his mature work. The earliest of them is the Geographer of the Rouen Gallery. (Fig. 1.)

* Read at the meeting of the Johns Hopkins Hospital Historical Club April 10, 1911.

[1] The two mendicants (Menippus and Aesop) and the Berlin del Borro (of somewhat doubtful authenticity), though allied to this group, should be separately considered.

The subject of this portrait is probably the same person as the one represented in the striking Pablillos de Valladolid (Fig. 2). The Bouffon Pernia (Fig. 3) and the Don Juan of Anstria (Fig. 4) complete the Buffoon Group.

The Dwarf pictures fall into two groups according to the predominance of portraiture or pathology. In the first group Velasquez has immortalized those of his dwarfed every-day companions whose deficiencies were only physical. Here belong the El Primo (Fig. 5), the Don Sebastian de Morra (Fig. 6), the Don Antonio d'Ingles (Fig. 7), and the Don Carlos and his Dwarf (Fig. 8). The Don Carlos in the Riding School in the Westminster Collection, includes, in the background two court dwarfs; and mention should be made of the portraits of two fragile, stunted, royal children (Philip Prosper, Royal Gallery, Vienna, and Don Carlos, Wallace Collection, London).

More striking is the group in which the monstrous predominates. These are the pictures it is hardest to imagine a painter producing; yet Velasquez seems to have painted these prodigies "with care and pleasure, just as he would have painted a pretty woman—without a thought." One recalls Charles Morice's remark about Cézanne "A potato is as significant for him as a human face."

The most remarkable of this group is the El Niño de Vallecas (Fig. 9). It has been said that one can hear this idiot dwarf's nasal whine. But in the El Bobo de Coria (Fig. 10), pathology has gained even more complete mastery. All that there is appaling in an idiot face is here. The crossed eyes, the pallor, the pathetic leer—nothing which fidelity of draughtsmanship dictates has been omitted. Somewhat less gruesome is the Idiot of the Vienna Museum (Fig. 11) (called also The Laughing Boy); but its authenticity is not beyond dispute.

In the picture called Las Meniñas (Fig. 12) two dwarfs appear; but so far from dominating the scene they are quite incidental. Maria Barbolo and Nicolasico Pertusato stand in the lower right-hand corner of the painting. The former has a cretinoid face and figure; the latter is a hydrocephalic, his miniature form emphasized by the great dog at his feet. The painting is of royal personages; the royal playthings happen to be of the group.

It certainly was not the fact that Velasquez' career narrowed the material at his disposal and forced this curious choice of subject on him; nor that the life of the world of his day was calculated to shrink his intellectual concerns. Consider, for a moment, the world in which he lived; and see if you would expect it to inspire a painter to devote his talents to dwarfs and fools. It was a world in which kingdoms were being daily destroyed, thrones reoccupied over night, territorial boundaries readjusted with every swing of the pendulum, armies slaughtered like rats, undreamed of countries explored, traditions ruthlessly set aside. Not many years before Velasquez' birth Copernicus and Columbus had created a new heaven and a new earth; and his life-time was pitched in that period of novelty and enthusiasm and intellectual adventure which has given us our own heritage of emancipation and at which we have never ceased to marvel. Erasmus, Savonarola, Melanchthon and Sir Thomas More had not long been dead: Zwingli, Knox, Calvin and Loyola were names fresh in memory and potent in influence; and the mantle of leadership had fallen on a host of Velasquez' contemporaries, all of them names for all time: Corneille, Racine, Molière, Descartes, Locke, Spinoza, Leibnitz, Milton, Bunyan, Pope, Swift, Dryden, Addison, Newton and Harvey. Not content with this exhibition of stars the managers of the political show had prepared a monster carnival of intrigue and slaughter in which Tilly, Wallenstein, Gustavus Adolphus, Cromwell, Richelieu, Mazarin and a host of others were taking part. Europe was adrip with blood; bivouacs were never quenched; every rising sun greeted a fresh hero of carnage and adventure. It is a task merely to list the events which brought about the separation of the Teutonic nations from Rome, and the transfer of progress from Italy and Spain to England and Holland. The pace had begun to tell, it is true, on Velasquez' own country; but though Spain was being now distanced she had recently known, and was still knowing, glorious times. Only 80 years before the painter's birth Don Carlos I of Spain had inherited the rule over more extensive dominions than any since the days of Charlemagne; and the fortunes of Spain had by no means waned when this extensively landed gentleman was chosen by the electors of Germany as Charles V of the Holy Roman Empire. In the life-time of Velasquez' parents Spain was in her hey-day; and the painter was born to an unexcelled heritage of national romance and honor and pride. He was destined, it is true, to see that heritage threatened; for, during his life-time, Spain and Italy—hitherto in the van of progress—began, like boys at the tag end of a parade, to lose interest in the line of march and wander up side alleys. The decadence was rapid. Spain, thanks to her king's conservative intellectual policy, failed to keep step with civilization; and not a great deal of water had flowed under the bridge before she had reached the level of a third-rate power. It is not without significance that, in the early days of her decadence, she should have produced one of the most progressive minds in all art; and that the spirit which, elsewhere in Europe, was touching science with a new life, should have singled out in Spain not a natural philosopher, but a painter. No one would, of course, for a moment expect European events—of no matter what magnitude—to have any *direct* influence on the artistic material chosen by a man like Velasquez. Court painter though he was, there was never any danger that he become an artist of the Washington-Crossing-the-Delaware type; he was immune to what has been so well called the anecdotal blight of the once-upon-a-time school. The exciting drama of European history did not disturb him in his studio; and it is not strange that this is so. But the drama was enacting, none the less; and Velasquez' choice of sordid material was forced on him by no lack of splendid show in the world without.

It must be remembered, too, that Velasquez by no means lived in obscurity. He became a part—in the end, a somewhat important part—of the distinguished and influential

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

life of Spain: and his career, from the first, lacked neither variety nor distinction. He was not even of humble parentage and Seville—the city of his birth—was the glory of the Spanish realms. His father, though poor, traced his ancestry through a Portugnese house to the kings of Alba Longa; and his Sevillan mother, whose name the son has immortalized, belonged to the hidalgas. His early advance was rapid. At 23—backed by influence—he had made for himself a secure place in Madrid; had painted the king's portrait; had been appointed court painter; and had been given a studio in the palace and a residence in the city. Painters were indeed in these days none too highly respected;[2] but Velasquez' position in Madrid gave him an opportunity for contact with men of distinction in the various walks of life. In 1628, for instance, he had the rare chance of a nine months' intimacy with Rubens, who had been sent to Spain on a diplomatic mission, but who managed, during his stay, to awaken Velasquez from his artistic lethargy and to persuade him to make the Italian journey.[3] In Rome he must have been a personage of some note; for he lived first at the Vatican, then at the Villa Medici, which was subsequently purchased by Colbert for the French Academy of Painting. He reached Spain again in 1631 and "His Majesty," writes Pacheco, "was greatly pleased at his return." Then followed 18 years of productive work, rewarded by many honors. In 1648 there was a second journey to Italy and, on his return, the appointment as Marshal of the Palace. It was in his capacity as Marshal that arrangements for a royal journey to the Pyrenees[4] fell to his lot, and here he contracted a "subtle, syncopal, tertian fever" of which he died (1660). Honors followed him to his death; and he was attended in his last moments by the Archbishop of Tyre and Patriarch of both Indies. Two years before he had been invested with the Habit of Santiago; but only after a long discussion, during which a council had reported that they "approved his age, purity of blood and lineage, but disapproved the nobility of his paternal and maternal ancestors." A dispensation for defective nobility was then issued by Pope Alexander VI; and Diego de Silva was created "hijo dalgo" by the king's order. The cross of the order of Santiago was conferred, after the artist's death, by order of the king.

[2] When Rubens, then in the full maturity of his powers and at the height of his glory, was sent by Holland to Madrid on a mission relating to the conclusion of peace between Spain and England, the Spanish king wrote, complaining that "such important matters should be confided to a painter . . . . , to a man of such an inferior position."

[3] It is interesting and significant that Velasquez escaped, in the words of de Beruete, being "seduced by the magic conceptions of Rubens." There is said to be one picture (a portrait of Philip IV on horseback in the Imperial Gallery of the Grand Duke of Tuscany in Florence) which was at first attributed to Rubens, but is now supposed to have been painted by Velasquez as a model for the Taccas bronze statue at Madrid. I know of no other painting about which similar confusion could possibly exist.

[4] The journey was made to celebrate the Treaty of the Pyrenees (ending a war waged by Mazarin against Spain) and the betrothal of the Infanta Maria Theresa to Louis XIV of France.

Honor, then, was his in abundance; and his life among men of distinction, both at the court and on his European journeys, was hardly one to contract his intellectual interests. This is, however, not quite the whole story, for in spite of the influential position which Velasquez early obtained at the Spanish court, it was among the court underlings that many of his days were spent. In the court registers he appears among the dwarfs, jesters and barbers of the palace. As late as 1637 a list was published containing the names of dwarfs, jesters, musicians, barbers, etc., to whom were given clothes of grace. Here one reads "the clothes of the barbers and of Diego Velazquez may be reduced to 80 Ducats, and those of the officials of the wardrobe to 70."[5] In the list of places assigned to the spectators of a bull fight (1642), Velasquez is put in the fourth tier with the servants of the grandees, the barbers of the palace and other underlings. During the painter's trip through Italy the Ambassador at Madrid wrote to the Archbishop of Pisa, à propos of a visit Velasquez was about to make: "Be careful to say 'you' to him and not 'your excellency'; for after all he is nothing but a painter."

One must, of course, bear in mind the position of relative honor held by dwarfs and jesters in the courts of Velasquez' day. Spain, indeed, rather outdid England and the rest of Europe in this matter; though royal fondness for miniature men was an old and general hobby. In Scandinavian mythology dwarfs originated as maggots in giants; but in actual life their acute and active minds, their sensitive natures, made the maggots and not the giants the choice of kings and queens. Not only were the pygmies royal favorites; some of them were noted characters and a few, able men. Men like Philetus of Cos, Vladislas Cubitas,—King of Poland—and Pēpin le bref, though of doll-like physique, were diminutive neither in mind nor in achievement. Strangely enough, however, the royal fancy did not always require an excess of mental endowment to offset the physical deficiencies. Bébé, for instance, the dwarf of Stanislaus of Poland, was practically an idiot; and the pet presented to Henrietta of France in a pie, could hardly have been highly regarded to be so lightly treated. Yet some of Velasquez' miniature associates were undoubtedly attractive and intelligent men. It is interesting to recall that Zuloaga, who has commemorated on canvas the repulsive features of his dwarfed servant, sometimes dreamed of collaborating with a great composer on an opera written about the life and death of that dwarf. "He was my servant," said Zuloaga. "A strange man, very hideous, physically distorted. But his life was wonderful. His death—he died of love."

The buffoons, too (*truhanes* or *hombres de placer*), possessing a sinister power, held a place in court by no means insignificant. "They represented," says Justi, "freedom of speech in its lowest degradation"; and, though employed ostensibly for royal amusements, they became a power by gaining the royal ear. Embassies were not infrequently entrusted to them; and instances are on record of wise men having played the fool in order to have the fool's influence with the

[5] The ducat was worth about 23 cents.

king. "A vaudeville supported by his Catholic Majesty." Beruete has called this group of miniature and clownish men: but Velasquez' classification with them must be interpreted in the light of the place they held in the court life of the time.

His choice of these bizarre types for portraiture is of course not unique in art. Carreño, Rubens, Fortuny, Zamacois and many others have produced pictures of dwarfs. But Velasquez alone has painted a large series of this kind; he alone has entrusted his fate in so large part to so precarious a medium; he alone has introduced such subjects into his best pictures—into the picture, indeed, which, if all else he did perished, would still entitle him to a high place in art. These are sufficiently striking facts. One does not overlook the other work that Velasquez did; but the dwarf and jester group cannot themselves be overlooked, nor regarded as incidental. They form a large, an integral part of his artistic output.

There is no warrant for assuming that Velasquez' peculiar choice of medical material in his art indicated any spirited interest in medicine. Such an interest, if it had existed, would hardly have confined itself to a restricted and revolting clinical field; it might have been expected, as Steen's did, to select some of the more human aspects of medical life—aspects more likely to awaken interest and more certainly suitable to the purposes of art. Spanish medicine was, indeed, in no condition to arouse any vivid enthusiasm. The uprising of the Germanic spirit in the North and the gradual degeneration of the South were giving a new direction to the history of science. Every one is familiar with the galaxy of medical stars flashing in the Netherlands, in England, in France and in Italy; but Spanish names, if they are known to us at all, hardly match those in the list which includes Boerhaave and Harvey. Even during the days of her political supremacy Spain seems to have failed singularly to beget physicians of the very first rank. Lisbon, Salamanca and Alcala produced, of course, medical men of some importance; but, aside from the Belgian-born Vesalius not a single Spaniard achieved immortality in a day when physicians of other European countries were writing their names for all time.[6]

Consider, too, how abruptly Velasquez turned his face on his artistic precedents in painting these pictures. Painting, in contrast with Castillian architecture and literature appeared late and developed slowly in Spain; and it continued to be hemmed in by the straitest conventions. The three schools (of Castille, of Andalusia and of Valencia) differed in many respects, but they were one in their devotional character. The church was the sole patron of art; and most Spanish painters spent a part of, many of them all, their lives in convents and cathedrals. "The chief end of the works of Christian art," wrote Velasquez' own father-in-law, "is to persuade men to piety and to bring them to God." "Even at Alcala and Salamanca," writes Sterling-Maxwell, "St. Jerome was always more popular than Cicero." Yet Velasquez, growing up in this tradition, became the painter of "sinners of the court rather than saints of the calendar."

It is interesting to speculate as to this extraordinary choice of subject on the part of a man of unexcelled powers, who lived in an exciting world—the friend of celebrities, the intimate of kings. Certainly such a man would hardly confine his artistic output to the still life, from which he learned his draughtsmanship; and line the galleries of Europe—as Weenix did—with melons and grapes that might have come from a country fair or with fish and sides of beef to rejoice any butcher's heart. Yet see how he did confine his interests. The insipid Hapsburg face he must, as court painter, reproduce; a task, in itself, not altogether promising, the degenerating Hapsburg kings of Spain being, at this time, in the suburbs of imperial melancholy.[7] Yet Velasquez, when free from this imposed task, did not flee to stirring subjects; he continued, in Beruete's phrase, to "chant a hymn to ugliness"; and after leaving the royal personage, whose features are familiar solely because Velasquez painted them and whose name has small title to remembrance save as the inventor of the *golilla*—a mode in collars—Velasquez goes to the degenerate playthings of this royal degenerate. It seems an obvious suggestion that the painting of these creatures was ordered by their melancholy owner and simply fell in Velasquez' day's work. Yet why did he lavish such care on them; if they repelled him, why did he not—as others had done—introduce them into groups where they could serve as foils for beauty? One is tempted to appeal to the melancholy genius of Spain, to the tendency to brood over the idea of death, which those authorized to speak regard as much more characteristic of the country than the notorious gaiety of southern Europe. Yet it is just this absence of any feeling on the subject, which impresses you strongly. It would be difficult to find a more perfect example of objective painting. Not only, are no distressing details of repulsive objects omitted; but what is much more striking, because much rarer, is the absence of all effort to give a tragic twist to things. The man who painted them might never have had an emotion, and seems indifferent about awakening any. He handled skulls, he fondled them; but never an "Alas, poor Yorick!" escaped his lips. One imagines him gazing at these living abortions with senses alert but with feelings all unstirred. And that, one may say again, is the attitude of science, not of art. No doubt he painted these pictures simply because he wanted to; no doubt, once dwarfs and jesters had aroused his interest, he gave absolutely no thought to their fitness as artistic material. Hidden, refined motives need not be sought for; but intellectual lethargy, said to be an Andalusian trait, is apparent. And that is the interesting light a consideration of this group of pictures throws on the man, marking him off from those who are interested, first,

[6] In the note on Spanish medicine, which is appended, I have indicated some of the important physicians of the time and their achievements. No epoch-making names occur; but it is of interest to see that a few important early contributions were made (note especially the institution of the *Hospital dels folls* at Valencia and the work of Andreas a Laguna in genito-urinary surgery).

[7] One of them (Philip II) on seeing a man laugh, said: "Either that man is mad or he has been reading Don Quixote."

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

in having something worthy to paint and only secondarily in painting it. Instead of selecting his material he allowed his material to select him. On opening his eyes in the morning dwarfs and jesters were the things in his field of vision; they satisfied his artistic demands, in which imaginative needs played little part. To their reproduction on canvas he gave a conscientious draughtsmanship and an infinite talent; in selecting them to paint at all he was intellectually indolent to a degree. Mr. Low has recently written of one of his friends: "He was a man (in Gautier's phrase) for whom the visible world really existed; and *therefore* he was inclined to give Velasquez the supreme place in art." Velasquez' visible world was peopled by deformed and clownish men; their existence was real for him; beyond such a world one imagines he seldom looked.

At any rate, the importance of these pictures in the history of art is of the greatest. They began a new era. One of them Giordano called the Theology of Painting; and though there is no agreement as to what he meant, there is general agreement that it was high praise. There are, of course, those now —there have always been those—who feel that the painting of deformed and clownish men is an artistic achievement of about equal value with learning to write with one's toes. Yet high praise—even worship—Velasquez has received from painters of varied temperaments. His voice—a modern voice in mediæval times, a scientific voice in art—has hushed a good deal of talk about beauty as the sole concern of art. He was not without his own artistic convictions. "I would rather," he said to some one who suggested Rubens as a model, "be the first of vulgar than the second of refined painters." He even had a formula ("Truth, not painting") which, though often quoted, may be made to mean whatever you like. Yet it is certain he did not take rules of thumb very seriously. One imagines his sombre face smiling quietly at formulæ. "A picture is a painted poem," said the ancient Chinese; "I celebrate myself and sing myself," shouted Walt Whitman; "Art is simply and solely the effective transmission of experience," writes Tolstoi; "Paint the soul, never mind the arms and legs," was the friar's advice to Fra Lippo Lippi; "There is no excuse for art, unless it present something different from nature," wrote Goethe. There are the formulæ; here are the paintings; and they do not fit. "Painting," Velasquez would probably have replied, in Corot's words, "is not so complicated as you make out"; or in Huysmann's, "I write what I have seen, what I have felt, what I have experienced, and I write it as well as I can, that is all."

Strangely enough, a Spanish poet (Quevedo) has used, in describing Velasquez, the very metaphor—almost the very words—which have come to stand for the Shakesperian attitude in art:

> "Then deem the picture—by the skill,
> That few shall reach and none surpass,
> Delighted and deluded still—
> The face of nature in a glass."

Great divergence of opinion exists as to the exact number of genuine Velasquez paintings extant. Twenty-four pictures, attributed to this artist in the early inventories of the palace, were destroyed in the fire at the Alcazar—among them three portraits of buffoons, descriptions of which (by Palermino) have survived. Beruete credits Velasquez with only 83 original paintings; Curtis describes a much larger number. In addition to the Menippus, Æsop and del Borro and to the portraits of sickly children (Philip Prosper and Don Carlos) there are 19 extant paintings belonging to the series of Jesters, Dwarfs and Idiots. The genuineness of Nos. 2, 5 and 19 is not beyond question; but in the case of the other 16 authenticity has been established.

PAINTINGS BY VELASQUEZ IN WHICH DWARFS, JESTERS AND IDIOTS ARE REPRESENTED.

I. Jesters:
- *1. Pablillos de Valladolid. Prado, Madrid.
- *2. Bouffon (Cristobal de Pernia). Prado, Madrid.
- *3. Don Juan of Austria. Prado, Madrid.
- *4. Portrait du Géographe. Rouen.

II. Dwarfs:
- *5. Antonio d'Ingles. Prado, Madrid.
- *6. El Primo. Prado, Madrid.
- *7. Don Sebastian de Morra. Prado, Madrid.
- *8. Carlos and his Dwarf. Copley Museum, Boston.
- °9. A Dwarf with dog and parrot. Gallery Lord Ashburton.
- °10. Two dwarfs leading a spotted hound. Louvre.
- °11. A Spanish court dwarf. Royal Museum, Berlin.
- 12. Olivares and Balthasar Carlos with dwarfs. Gallery, Duke of Westminster, Grosvenor House.
- °13. A dwarf seated reading. Gallery Señor Salamanca, Madrid.
- °14. Prince Balthasar in riding school (similar to 12). Wallace Gallery.
- *15. Las Meniñas. Prado, Madrid.
- 16. Die Infantin Margarete und die Zwergin. Maria Barbola.

III. Idiots:
- *17. El Niño de Vallecas. Prado, Madrid.
- *18. El Bobo de Coria. Prado, Madrid.
- *19. Der lachende Bursche (or der Idiot). Royal Gallery, Vienna.

Pictures marked * are here reproduced; the mark ° before the title signifies that the gallery stated may not be the present site of the picture in question.

NOTE ON SPANISH MEDICINE IN THE DAYS OF VELASQUEZ.

Though Spanish names of the very first importance are wanting, Spanish physicians and surgeons in the XVI century were sufficiently active to have left their mark on the times. As early as 1545 a treatise on the operation for vesical calculus was in circulation (Juan Gutièrrez); and a number of publications appeared on the treatment of wounds and on trepanation. These treatises were written by the professors at Salamanca, at Seville, at Lisbon, and by the court physicians. One of the important monographs was by Bartholomé de Aguero (1531-1597), professor at Seville, who was a strong exponent of the immediate closure of wounds; in fresh wounds he advocated protection from air and the use of coagulating and drying materials. In Spain, as elsewhere, much energy was devoted to maintaining the traditions and recording the history of medicine; commentaries and translations were numerous; Hippocrates, Galen and Avicenna had their exponents. The author of one of the histories of medicine (Lusitanius of Lisbon) deserves especial mention for

having advanced what is practically the accepted theory of "an epidemical constitution" and "a contagium."

The Spanish Galen (Andreas a Laguna) was an interesting figure of the times. Most of his life was spent at the court of Charles V. He was a physician, philosopher and statesman who lost his life in the plague at Metz. He wrote one of the earliest treatises on the treatment of urethral stricture with bougies. His book entitled "Methodus cognoscendi exstirpandique excrescentes in vesicae collo carunculas" must have been one of the very early works on the subject.

The most interesting figure was, of course, Vesalius. He was born in Brussels and held professorships in Padua, Bologna and Pisa. On the abdication of Charles V, Vesalius, who had accompanied him into Spain, went into the service of Philip II. Here, the court duties, the jealousy of Spanish physicians, the hatred of the clergy and the lack of anatomical material preyed on his melancholy temperament, and he decided to leave Spain and make a crusade to Jerusalem. On the death of Fallopius, he was called to succeed him in the Paduan professorship, but was shipwrecked on the way home and died in hunger and misery.

One of the most important contributions of Spain to mediæval medicine was the establishment of the *Hospital dels folls at* Valencia. It was here that probably the first effort was made to treat psychopathic patients reasonably and humanely. The hospital was founded in 1409 by Bernardo Andreu, following a mission conducted by the brothers Gilaberto Jafré in the cathedral. According to Lope (*Las Locos de Valencia*) this hospital was a show place and much frequented by visitors.

Other names that should be mentioned are:

Dionista Daça Chacon: Physician to Charles V, Philip II, Don Carlos and Don Juan of Austria; advocated non-poisonous nature of gunshot wounds.

Francisca Lopez: Physician of Charles V. Extracted Avicenna's Kanon.

Vallesius: Professor at Alcala, published explanations of the aphorisms, later quoted by Boerhaave.

Luis de Lemos: Professor at Salamanca; one of the first to make inquiry into the authenticity of the Hippocratic writings.

Roderigo a Castro: Author of an important treatise on gynecology: De universa mulierum medicina opus absolutissimum! 1603.

Mercado: Treatises on typhus, gynecology, obstetrics and children's diseases; famous work on the garrote.

Diaz: Professor at Alcala, known for writings on kidney diseases and the relation of vesical calculus to gout.

Boccangelino: One of the best authors of the XVI century on the plague.

Francisco Valles: One of the earliest pathological anatomists who, with Pedro Ximenes, attempted to elucidate Galens, "De locis affectis," by anatomical work.

DESCRIPTION OF PLATES.

Fig. 1.—"Portrait d'homme dissertant sur une mappemonde." Museum at Rouen. Also known as "Portrait de Cristophe Colomb" and as "Portrait du Géographe." Attributed to Ribera and to Carreño. Supposed by Bonnat and Madrazo to have been retouched by Velasquez many years after it was painted, with Pablillos de Valladolid for a model. "Le mouvement de la main devient tout naturellement un geste de moquerie à l'addresse des navigateurs et de ces découvreurs de terres inconnues qui promènent leur curiosité inquiète autour de la mappemonde, et le rire épanoui du bouffon se gausse de leurs déconvenues." (Louis Gonze: Gazette des Beaux-Arts, 1893.)

Fig. 2.—Pablillos de Valladolid, sometimes called The Comedian. Subject supposed to be the same as that of the Rouen "Portrait du Geographe."

Fig. 3.—Portrait of the Bouffon, Pernia. Prado, Madrid. This portrait is not regarded as a genuine Velasquez by Beruete.

Fig. 4.—Don Juan of Austria, Bouffon of Philip IV, the Prado, Madrid. Don Juan of Austria was a natural son of Charles V. The name was also borne by a bastard son of Philip IV and the actress la Calderona.

Fig. 5.—El Primo. The Prado, Madrid.

Fig. 6.—Don Sebastian de Morra. The Prado, Madrid. The original was injured by fire and many of its details blurred.

Fig. 7.—Portrait of Antonio d'Ingles. The Prado, Madrid. Antonio was the dwarf of Philip IV.

Fig. 8.—Carlos and his Dwarf. Copley Museum, Boston.

Fig. 9.—El Niño de Vallecas. The Prado, Madrid.

Fig. 10.—El Bobo de Coria. The Prado, Madrid.

Fig. 11.—The Laughing Boy. Called also The Idiot. Royal Gallery, Vienna.

Fig. 12.—Las Meniñas. Called by Giordano The Gospel, or Theology of Painting. Las Meniñas were girls who had not yet assumed the womanly heels: they wore neither mantle nor hat and like the pages in France, served their King and Queen. In the center of the picture stands the Infanta Maria Margarita. She is receiving a cup of water from the Queen's handmaid, Doña Maria Augustina Sarmiento. To her left Doña Isabel de Velasco dropping a curtsy. The two dwarfs Maria Barbolo (cretinoid) and Nicolasico Pertusato (hydrocephalic). A woman and a *guardadamas* in mid-background; far back on stairway the Queen's aposentador. In the mirror the reflections of the King and Queen.

STUDIES IN GLYCOSURIA.

I. ETHER GLYCOSURIA.

By John H. King, M. D.,
Associate in Pathology, The Johns Hopkins University
and
B. S. Chaffee, D. B. Anderson and L. H. Redelings.
(*From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins Medical School.*)

The first investigator to call attention to the fact that a reducing body may appear in the urine after etherization was Ruschhaupt (1), who observed glycosuria, in two instances, in rabbits under ether. The presence of reducing materials in the urine of dogs following ether anæsthesia was independently observed by Geis and White and P. B. Hawk. Then Seelig (2) undertook a study of the question. In an early paper he drew attention to several interesting results. This author found that ether inhaled for a longer or shorter time caused a marked glycosuria in healthy dogs. The time of appearance

of the sugar was varied. It was found as early as ten minutes after the beginning of the anæsthetic in one case, and as late as two hours in another. In general a reducing body will appear in the urine at the end of one hour if the narcosis is deep.

The quantity of reducing body in the urine can, with little diuresis, amount to 10 per cent, but the average is about 3 or 4 per cent. Seelig thought that the glycosuria increased with the length of the experiment. The glycosuria lasts only a short time. It disappears on an average of about 7 hours after the discontinuance of the anæsthetic, but may last as long as 16 hours or even 24 hours. The glycosuria depends upon a hyperglycæmia, as the sugar in the blood was found increased under the influence of the anæsthetic. The increase in the blood-sugar, however, Seelig points out may not be very striking.

If the glycosuria were dependent upon simple filtration of dextrose through the kidney for its occurrence, then the sugar in the blood should be less after etherization. Such has never been found to be the case, in the author's experiments, nor in ours. Seelig thinks that there might be some participation of the kidney in the process, as he often found albumin in the urine.

After anæsthesia, Seelig states that the glycogen in the liver is less, pointing to this organ as the direct cause of the hyperglycæmia, by increased conversion of glycogen into glucose. He points out some further interesting results which it will be found more advantageous to consider later in our paper. Furthermore, in a second paper, Seelig considers the influence of diet upon the occurrence of this type of glycosuria. Here again it seems preferable to reserve this discussion for later consideration.

Hawk (3) pointed out that during and following ether anæsthesia the urine acquired considerable reducing power, but he did not consider that there occurred a sufficient hyperglycæmia to account for it.

Macleod (4) likewise observed the occurrence of glycosuria under ether, but also regards its influence on the blood-sugar as of very slight extent. The cause, he says, is a mystery. He regards the glycosuria as either due to some permeability of the renal epithelium, or that the anæsthetic may act upon the sugar combination in the blood, increasing the amount of free sugar, which is then immediately filtered off in the urine. A rather interesting point is raised in this paper as to whether the reducing property acquired by the urine is due entirely to dextrose or in part to some other substance. Upon this point our results may throw some light.

Underhill (5) states that ether does not cause any notable change in the sugar content of the blood, when employed in the degree of slight anæsthesia, nor does it induce the passage of a reducing body into the urine though the anæsthesia be prolonged 3-4 hours.

It would seem quite well established that ether, in common with several other drugs, possesses the power of inducing the passage of sugar into the urine.

Experimental.—It seemed desirable before investigating more minutely the mechanism of ether glycosuria to make a few preliminary experiments to confirm its appearance. Accordingly, several dogs were anæsthetized with the ordinary routine ether for anæsthesia. The anæsthesia was deep in every case and the dogs chosen were all healthy active animals. It was found that a very definite reducing property was acquired by the urine after ether anæsthesia.

EXPERIMENT No. 1.—Dog, No. 80. Female. Diet: Meat and bread. Gave 300 cc. of water by stomach tube, 45 minutes before beginning of anæsthesia. Anæsthesia, 10 a. m. to 12 m. Amount of ether given, 150 cc. The urine drawn just prior to beginning of anæsthesia was negative to Fehling's test. At the end of 1 hour, animal was catheterized and 5 cc. of urine obtained. This completely reduced Fehling's solution in a test tube. No. albumin. Catheterized at 3.30 p. m. Urine, 38 cc. Fehling's +. Catheterized at 4.45 p. m. Urine, 35 cc. Fehling's +. June 28, 1910, catheterized at 9 a. m. Urine, 120 cc. Fehling's +.

Remarks.—Ether caused the appearance in the urine of a reducing substance at the end of 1 hour, which persisted for 24 hours.

EXPERIMENT No. 2.—Dog, No. 112. Diet: Meat and bread. Animal was anæsthetized for 5 hours. Urine drawn at end of 20 minutes, after beginning of anæsthesia, reduced Fehling's solution very strongly. Urine drawn by catheter, 36 hours after end of anæsthesia, did not reduce Fehling's solution.

EXPERIMENT No. 3.—Dog, No. 80. Female. Diet: Meat and bread. Gave dog ether from 10 a. m. to 11.30 a. m. Amount, 150 cc. Urine drawn before beginning of anæsthesia was negative to Fehling's, and the polariscope. Urine drawn at the end of anæthesia turned the plane of polarized light 1° to right. A specimen of this urine greatly reduced Fehling's solution.

Some yeast was added to a specimen of this urine and allowed to ferment for 22 hours. At the end of this time, the urine was filtered and examined by the polariscope. The plane of polarized light was not turned at all. The urine was also negative for Fehling's. This demonstrates clearly that the reducing property acquired by the urine is due to dextrose.

EXPERIMENT. No. 4.—Dog, No. 80. Female. Diet: Meat and bread. Dog was given ether from 9.05 to 10.05 a. m. Amount, 13.5 cc. Urine drawn before beginning of anæsthesia was negative for Fehling's. Catheterized at 3 p. m. and 105 cc. of urine obtained. Tested quantitatively by Benedict's method, it showed 0.7304 gm. dextrose.

These experiments will suffice to confirm the previous findings in the literature that ether causes a definite glycosuria which may make its appearance as early as 20 minutes after beginning the anæsthesia, and disappears by the end of 24 hours. The reducing property of the urine is due to dextrose.

To explain the occurrence of ether glycosuria, it is obviously first necessary to know what changes the anæsthetic has upon the sugar content of the blood. Previous experiments from the literature indicate that a hyperglycæmia precedes (6) and causes the appearance of sugar in the urine. The results are, however, not in great harmony, and an accurate study of the conditions in the blood seemed desirable at this point. Accordingly several experiments were made to ascertain whether a hyperglycæmia occurred after ether anæsthesia and how large an increase in sugar in the blood resulted.

Method.—Healthy adult female dogs were chosen for these experiments. They were all fed upon the same diet, namely, 200 gm. of lean meat daily, and as much water as they chose to drink. Each experiment was conducted in the following manner: Under aseptic conditions and local anæsthesia 50 cc. of blood was drawn from the jugular vein into a weighed Erlenmeyer flask containing 5 cc. of 1 per cent sodium oxylate. The whole was then weighed and the weight of the blood thus obtained. The animal was then anæsthetized with ether for two hours and at the end 50 cc. more of blood drawn from the same vein under the same procedure. The animal was then placed in a cage and the urine collected for 24 hours in a receptacle containing 5 cc. of toluol. The blood was examined for sugar by the excellent method of Oppler-Bertrand (7), and the urine for sugar by the method of Benedict and the polariscope.

A word must be said here regarding the influence of diet upon the occurrence of ether glycosuria. Seelig (9) reports that if animals are fed for a long time on carbohydrate diet they do not react to ether by showing a glycosuria. The time necessary for such feeding is generally 3-4 weeks for a medium-sized dog. Occasionally the condition can be brought about in 10 days. However, if fed on a meat diet, the animal responds to the administration of ether by a well-marked glycosuria. In all of our experiments, with the exception of the preliminary ones, the animals were fed upon the same diet, namely, 200 gm. of lean meat daily.

The results of the experiments are given below.

Experiment No. 5.—Female. Dog, No. B 18. Drew blood from right jugular vein before anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 112.30600
	Weight of flask + NaOx	= 54.86300
	Weight of blood	= 57.44300

Percentage of sugar = 0.059 per cent dextrose.

Etherized dog for 2 hours, using 250 cc. of ether and at end drew off blood as above.

		gm.
2.	Weight of flask + NaOx + blood	= 106.17210
	Weight of flask + NaOx	= 54.52900
	Weight of blood	= 51.64310

Percentage of sugar = 0.141 per cent dextrose.

Increase in sugar of blood due to ether anæsthesia = 0.082 per cent dextrose.

Remarks.—A marked increase in the percentage of sugar in blood.

Experiment No. 6.—Dog, No. B 15. Female. Drew blood from right jugular vein, before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 109.09420
	Weight of flask + NaOx	= 58.21425
	Weight of blood	= 50.77995

Percentage of sugar = 0.031 per cent dextrose.

Etherized dog for 2 hours, using 250 cc. of ether and at end drew off blood as above.

		gm.
2.	Weight of beaker + NaOx + blood	= 107.61190
	Weight of beaker + NaOx	= 58.29200
	Weight of blood	= 49.31990

Percentage of sugar = 0.215 per cent dextrose.

Increase in sugar of blood due to anæsthetic = 0.184 per cent. Urine was drawn by catheter at end of anæsthesia and 40 cc. obtained. This strongly reduced Fehling's solution.

Experiment No. 7.—Dog, No. B 15. Female. Blood taken from left jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 115.22300
	Weight of flask + NaOx	= 62.49020
	Weight of blood	= 52.73280

Percentage of sugar = 0.058 per cent.

Etherized dog for 2 hours, using 250 cc. of ether, and at end drew off blood as above.

		gm.
2.	Weight of flask + NaOx + blood	= 110.96920
	Weight of flask + NaOx	= 58.13490
	Weight of blood	= 52.83430

Percentage of sugar = 0.113 per cent.

Increase in sugar in blood due to anæsthetic = 0.055 per cent.

Experiment No. 8.—Dog, No. B 63. Female. Blood taken from right jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 83.47240
	Weight of flask + NaOx	= 31.34960
	Weight of blood	= 52.12280

Percentage of sugar = 0.041 per cent dextrose.

Etherized dog for 2 hours, using 250 cc. of ether, and then drew blood from vein as above.

		gm.
2.	Weight of flask + NaOx + blood	= 93.61430
	Weight of flask + NaOx	= 40.85850
	Weight of blood	= 52.75580

Percentage of sugar = 0.159 per cent.

Increase in sugar in blood due to anæsthetic = 0.118 per cent. The urine was collected for 24 hours. Amount, 230 cc., clear, no albumin. Sugar, 2.5596 gm.

Experiment No. 9.—Dog, No. B 65. Female. Blood taken from right jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 87.82200
	Weight of flask + NaOx	= 35.63600
	Weight of blood	= 52.18600

Percentage of sugar = 0.055 per cent dextrose.

Etherized dog for 2 hours, using 250 cc. of ether, and then drew blood from vein as above.

		gm.
2.	Weight of flask + NaOx + blood	= 87.29390
	Weight of flask + NaOx	= 36.79590
	Weight of blood	= 50.49800

Percentage of sugar = 0.111 per cent dextrose.

Increase in sugar in blood, due to anæsthetic = 0.056 per cent. Urine collected for 24 hours. Amount, 480 cc., no albumin. Sugar, 1.0745 gm.

EXPERIMENT No. 10.—Dog, No. B 66. Female. Blood taken from right jugular vein, before beginning of experiment.

		gm.
1.	Weight of flask + NaOx + blood	= 88.22560
	Weight of flask + NaOx	= 38.36390
	Weight of blood	= 49.86170

Percentage of sugar in blood = 0.045 per cent dextrose.

Dog etherized for 2 hours, using 250 cc. of ether, and then blood drawn from vein as above.

		gm.
2.	Weight of flask + NaOx + blood	= 86.76400
	Weight of flask + NaOx	= 36.78050
	Weight of blood	= 49.98350

Percentage of sugar in blood = 0.094 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.040 per cent dextrose. The urine showed a positive reduction to Fehling's test.

These experiments demonstrate conclusively that in healthy dogs following the administration of ether to the point of deep anæsthesia there occurs an increase of sugar in the blood, which then passes into the urine and causes the appearance of a reducing body in that fluid. In no case did sugar appear in the urine, unless the percentage of sugar in the blood was above normal.

These results are collected into tabular form for their more ready interpretation.

TABLE No. 1.

Dog.	Gender.	Diet.	Anæsthesia.	Length of anæsthesia.	Percentage of sugar in blood before anæsthesia.	Percentage of sugar in blood after anæsthesia.	Percentage of increase in sugar in blood.	Sugar in urine.
B 18	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.059%	0.141%	0.082%	+
15	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.031%	0.215%	0.184%	+
15	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.058%	0.113%	0.055%	+
B 63	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.041%	0.159%	0.118%	+ 2.560 gm. dextrose.
B 65	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.055%	0.111%	0.056%	+ 1.075 gm. dextrose.
B 66	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.045%	0.094%	0.049%	+

Seelig (9) was of the opinion that the extent of the glycosuria depended upon the amount of the anæsthetic used, *i. e.*, that the longer the anæsthesia was continued the greater became the percentage of sugar in the urine.

Some experiments were conducted to test this point, and the results are given below:

EXPERIMENT No. 11.—Dog, No. B 61. Blood was taken from the right jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 87.47120
	Weight of flask + NaOx	= 36.74400
	Weight of blood	= 50.72720

Percentage of sugar in blood = 0.034 per cent dextrose.

Dog etherized for 30 minutes, using 25 cc. of ether. Animal was just under the influence of the anæsthetic. Blood was taken at end of anæsthesia from right jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 93.215900
	Weight of flask + NaOx	= 39.448900
	Weight of blood	= 53.767000

Percentage of sugar in blood = 0.087 per cent dextrose.

The increase in sugar in the blood, due to the anæsthetic = 0.053 per cent dextrose. Urine, 150 cc. No reducing bodies.

The same experiment was repeated.

EXPERIMENT No. 12.—Dog, No. B 61. Female. Animal was bled from right jugular vein before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 119.27020
	Weight of flask + NaOx	= 70.05150
	Weight of blood	= 49.21870

Percentage of sugar in blood = 0.046 per cent dextrose.

Dog was then etherized for 30 minutes with 25 cc. of ether. At end of anæsthesia, animal was bled from right jugular vein as above.

		gm.
2.	Weight of flask + NaOx + blood	= 111.08180
	Weight of flask + NaOx	= 60.47790
	Weight of blood	= 50.60390

Percentage of sugar in blood = 0.076 per cent dextrose.

Increase in sugar in blood, due to anæsthetic = 0.030 per cent. Urine collected for 24 hours. Amount 280 cc. Acid, albumin none, sugar none.

A second experiment was performed on the same dog, using 100 cc. of ether.

EXPERIMENT No. 13.—Blood taken before anæsthesia from right jugular vein.

		gm.
1.	Weight of flask + NaOx + blood	= 90.20300
	Weight of flask + NaOx	= 41.23510
	Weight of blood	= 48.96790

Percentage of sugar in blood = 0.043 per cent dextrose.

Dog etherized for ½ hour, using 100 cc. of ether. Dog was deeply under. Blood taken at end of anæsthesia from right jugular vein as above.

		gm.
2.	Weight of flask + NaOx + blood	= 85.19860
	Weight of flask + NaOx	= 39.77230
	Weight of blood	= 45.42630

Percentage of sugar in blood = 0.089 per cent.

Increase in sugar of blood, due to anæsthetic = 0.046 per cent dextrose. Urine collected for 24 hours, 610 cc. Albumin, 0; sugar, +. (Trace by Fehling's test.)

The results of all these experiments show that the extent of the hyperglycæmia is more or less dependent upon the amount of the anæsthetic used and the length of the anæsthesia.

TABLE No. 2.

Dog.	Gender.	Diet.	Anæsthesia.	Amount of ether used.	Time of anæsthesia.	Increase in sugar in blood.	Sugar in urine.
B 61	Female.	200 gm. of lean meat daily.	Ether.	25 cc.	30 min.	0.053%	Negative.
B 61	Female.	200 gm. of lean meat daily.	Ether.	25 cc.	30 min.	0.030%	Negative.
B 61	Female.	200 gm. of lean meat daily.	Ether.	100 cc.	30 min.	0.043%	+
B 15	Female.	200 gm. of lean meat daily.	Ether.	250 cc.	2 hrs.	0.184%	+
B 63	Female.	200 gm. of lean meat daily.	Ether.	250 cc.	2 hrs.	0.118%	+

The occurrence of a hyperglycæmia naturally suggests that we turn our attention to the liver as the most probable organ for its source. What effect does ether have upon the glycogen content of this organ? Seelig (10) reports that the percentage of glycogen in the liver is diminished after etherization. Another method of investigating the question appealed to us: What would be the effect of removal of the liver from the circulation, upon the occurrence of ether glycosuria? This condition could be brought about by establishing an Eck fistula; then, after the animal had recovered from the effects of the operation, the study could be carried out in the same manner as outlined in the previous experiment. The results should indicate conclusively to what extent the liver entered into the mechanism of ether glycosuria.

The experiments are given below. All the animals were upon the same diet, namely, 200 gm. of lean meat daily.

Experiment No. 14.—Dog, No. B 36. Female. An Eck fistula was made for us by Drs. Bernheim and Stone. The animal made an excellent, immediate recovery and was allowed to recuperate for one week. During this period, the dog was given a liberal amount of bones and water with the regulation 200 gm. of meat. Then she was operated upon aseptically and 50 cc. of blood withdrawn from the right jugular vein before beginning of the anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 94.24300
	Weight of flask + NaOx	= 44.40810
	Weight of blood	= 49.83490

Percentage of sugar in blood = 0.055 per cent dextrose.

Dog was then etherized for 2 hours, using 250 cc. of ether, and then blood was taken from right jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 121.50790
	Weight of flask + NaOx	= 66.85840
	Weight of blood	= 54.64950

Percentage of sugar in blood = 0.0779 per cent dextrose.

Increase in sugar in blood = 0.022 per cent dextrose, due to anæsthetic. No sugar in the urine.

Remarks.—The increase is very much less than when the liver is in the circulation.

Experiment No. 15.—Same dog was used again after a week's rest. No. B 36. Female. Blood taken from right jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 108.91390
	Weight of flask + NaOx	= 61.19210
	Weight of blood	= 47.72180

Percentage of sugar in blood = 0.064 per cent dextrose.

Animal was etherized for 2 hours, using 250 cc. of ether, and then bled from right jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 120.32900
	Weight of flask + NaOx	= 66.89800
	Weight of blood	= 53.43100

Percentage of sugar in blood = 0.089 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.025 per cent dextrose. No sugar in the urine.

Remarks.—Here again the increase in sugar in blood after anæsthesia is strikingly less than when the liver is in the general circulation.

The dog was turned over to Dr. Whipple for further experiments, at the conclusion of which the animal was killed and a splendid Eck fistula was found to have exsited.

A third experiment was conducted to further confirm these results.

Experiment No. 17.—Dog, No. B 48. Female. Weight 25 pounds. An Eck fistula was established upon this animal by Drs. Bernheim and Stone. The animal recovered well, and was treated post-operatively exactly as in the previous experiment. Blood was taken from right jugular vein before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 89.62300
	Weight of flask + NaOx	= 39.43460
	Weight of blood	= 50.18840

Percentage of sugar in blood = 0.066 per cent dextrose.

Dog was then etherized for 2 hours, using 250 cc. of ether, and then bled from the right jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 86.95500
	Weight of flask + NaOx	= 39.97320
	Weight of blood	= 46.98180

Percentage of sugar in blood = 0.093 per cent dextrose.

Increase in sugar in blood, due to anæsthetic = 0.027 per cent dextrose. No sugar in the urine.

A fourth experiment confirmed the preceding ones.

Experiment No. 18.—Dog, No. B 48. Female. Dog bled from left jugular vein, before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 95.68100
	Weight of flask + NaOx	= 46.64100
	Weight of blood	= 49.04000

Percentage of sugar in blood = 0.059 per cent dextrose.

Dog given ether for 2 hours, using 250 cc., and then bled from left jugular vein at end of anæsthesia.

		gm.
2.	Weight of flask + NaOx + blood	= 72.07830
	Weight of flask + NaOx	= 39.42550
	Weight of blood	= 32.65280

Percentage of sugar in blood = 0.050 per cent dextrose.

Remarks.—Here there is no increase in sugar in blood after ether, but a slight decrease *i. c.* 0.009 per cent dextrose.

These experiments suffice to show what part the liver takes in the mechanism of ether glycosuria. When the liver is removed from the circulation and consequently from the effect of the anæsthetic, there occurs practically no change in the percentage of sugar in the blood. This, taken in conjunction with Seelig's findings of a diminished glycogen content of the liver following ether anæsthesia, establishes the liver as the organ furnishing the increased sugar to the blood. Of course some circulation reaches the liver through the hepatic arteries, and this may account for the very slight change in the percentage of the blood-sugar, but other experiments in which the hepatic artery was tied and cut indicate that the influence of the hepatic artery is very slight.

A table of the results of these experiments is given below.

TABLE No. 3.

ECK FISTULA DOGS.

Dog.	Gender.	Diet.	Anæsthesia.	Length of anæsthesia.	Percentage of sugar in blood before anæsthesia.	Percentage of sugar in blood after anæsthesia.	Percentage of increase in sugar in blood.	Sugar in urine.
B 36	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.055%	0.077%	0.022%	–
B 36	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.064%	0.089%	0.025%	–
B 48	Female	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.066%	0.093%	0.027%	–
B 48	Female.	200 gm. of lean meat daily.	Ether (250 cc).	2 hrs.	0.059%	0.050%	0.009%	–

In regard to the causes which induce the liver, under the influence of ether, to raise the sugar content of the blood, the literature is in much disagreement.

Edie (10) thinks that in an allied condition of asphyxia glycosuria, the cause lies in the presence of an excess of carbon-dioxide in the blood and tissues and not a poverty of oxygen.

Macleod (11) states that in asphyxia glycosuria, if the splanchnic fibers to the liver are severed, no glycosuria results. He also has demonstrated the presence of glycogenetic fibers to the liver in the splanchnics.

Moore and Roof (12) suggest that anæsthetics possess the power of combining with tissue protein, and in this way limiting the activity of the bioplasm, and its power of combining with bodies for the purpose of metabolism.

Lepine and Boulud (13) state that glycosuria in asphyxia is caused by lack of oxygen, which results in the production of leucomaines which interfere with glycolysis.

Edie (14) further suggests that the anæsthetic attracts the sugar containing substances in the tissues, setting free sugar.

Seelig (15) claims to be able to remove the effects of ether by intravenous infusions of oxygen.

Thus it is evident that the suggestions as to the cause of ether glycosuria can be largely grouped into three categories:

(1) Due to excess of carbon-dioxide.

(2) Due to poverty of oxygen.

(3) Action through the splanchnic.

In regard to the first suggestion, it was generally noted that the blood taken at the end of anæsthesia was quite red and did not suggest a high content of carbon-dioxide.

Further, Seelig did not notice any degree of asphyxia in his animals and does not give much consideration to this explanation.

As regards the administration of oxygen with the ether, we have not been able to prevent the occurrence of a glycosuria by such a procedure.

The control of many functions of glands by nerves is such a well-established process in the body that the possibility of ether acting through the mediation of the splanchnic nerve seemed worthy of study, especially in view of the results of the splendid experiments of Macleod (17), in which he demonstrated the presence of glycogenetic fibers in these nerves.

Accordingly, experiments were undertaken after the following schema:

(1) Dogs were anæsthetized as above, to determine their initial hyperglycæmia.

(2) Then they were operated upon, and the splanchnic fibers going to the liver cut, together with the hepatic artery. It was found that many of the fibers were so intimately associated with this artery that they could not be severed without also cutting the artery.

(3) After the animal had recovered, the effect of ether was again tried.

The results are given in the protocols below.

EXPERIMENT No. 19.—Dog, No. B 63. Female. Diet: 200 gm. lean meat daily. Dog bled from right jugular vein before starting anæsthetic.

		gm.
1.	Weight of flask + NaOx + blood	= 83.47240
	Weight of flask + NaOx	= 31.34960
	Weight of blood	= 52.12280

Percentage of sugar in blood = 0.041 per cent dextrose.

Dog was anæsthetized for 2 hours, using 250 cc. ether, and then bled from same vein.

		gm.
2.	Weight of flask + NaOx + blood	= 93.61430
	Weight of flask +	= 40.85850
	Weight of blood	= 52.75580

Percentage of sugar in blood = 0.159 per cent dextrose.

Increase in sugar of blood, due to anæsthetic = 0.118 per cent dextrose. The urine was positive to Fehling's test.

The dog was operated upon after a few days' rest, and the splanchnics cut, together with the hepatic artery as described

above. After a week's rest, the dog was then subjected to the ether experiment in same manner as before. Blood was drawn from the left jugular vein, before beginning the anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 89.47000
	Weight of flask + NaOx	= 38.61760
	Weight of blood	= 50.85240

Percentage of sugar in blood = 0.040 per cent dextrose.

Dog was then anæsthetized for 2 hours, using 250 cc. ether, and bled at end of anæsthesia from left jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 92.09410
	Weight of flask + NaOx	= 41.39570
	Weight of blood	= 50.69840

Percentage of sugar in blood = 0.144 per cent dextrose.

Increase in sugar in blood, due to anæsthetic = 0.104 per cent dextrose. Urine was positive for Fehling's test.

Remarks.—Cutting the splanchnics had practically no effect on the occurrence of ether glycosuria, as shown by the table.

	Per cent dextrose.
Increase in sugar in blood before cutting splanchnics	= 0.118
Increase in sugar in blood after cutting splanchnics	= 0.104

Another experiment was performed under the same conditions.

Experiment No. 20.—Dog, No. B 65. Female. Dog was on diet of 200 gm. of lean meat daily. Blood taken from right jugular vein before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 87.82200
	Weight of flask + NaOx	= 35.63600
	Weight of blood	= 52.18600

Percentage of sugar in blood = 0.055 per cent dextrose.

Dog was then anæsthetized for 2 hours, using 250 cc. of ether, and bled from right jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 87.29390
	Weight of flask + NaOx	= 36.79590
	Weight of blood	= 50.49800

Percentage of sugar in blood = 0.111 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.056 per cent dextrose. Urine showed 1.0745 per cent dextrose.

Animal was allowed to recover for a week and then operated upon and the splanchnics cut, together with the hepatic artery. After a few days' rest the animal was again subjected to the ether experiment as above. Blood was taken from the left jugular vein before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 96.54570
	Weight of flask + NaOx	= 45.73080
	Weight of blood	= 50.81490

Percentage of sugar in blood = 0.037 per cent dextrose.

Dog was then anæsthetized for 2 hours, with 250 cc. of ether, and at end of anæsthesia blood was drawn off from left juglar vein.

		gm.
2.	Weight of flask + NaOx + blood	= 104.39320
	Weight of flask + NaOx	= 53.28520
	Weight of flask	= 51.10800

Percentage of sugar in blood = 0.114 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.077 per cent dextrose. Urine showed 2.175 gm. dextrose.

Remarks.—The cutting of the splanchnics had no appreciable influence upon the glycosuria caused by the ether.

	Per cent dextrose.
Increase in sugar in blood before cutting splanchnics	= 0.056
Increase in sugar in blood after cutting splanchnics	= 0.077

Another experiment was performed under the same conditions.

Experiment No. 21.—Dog, No. B 66. Female. Dog on diet of 200 gm. of lean meat daily. Dog bled from right jugular vein before beginning anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 88.22560
	Weight of flask + NaOx	= 38.36390
	Weight of blood	= 49.86170

Percentage of sugar in blood = 0.045 per cent dextrose.

Dog was then etherized for 2 hours, using 250 cc. of ether, and bled from the right jugular vein at end.

		gm.
2.	Weight of flask + NaOx + blood	= 86.76400
	Weight of flask + NaOx	= 36.78050
	Weight of blood	= 49.98350

Percentage of sugar in blood = 0.094 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.049 per cent. Urine was positive to Fehling's test.

Dog was then allowed to recover for about a week and then operated upon as in previous experiments. After a week's recovery, the ether experiment was again repeated. Blood taken from right jugular vein, before beginning of anæsthesia.

		gm.
1.	Weight of flask + NaOx + blood	= 90.04270
	Weight of flask + NaOx	= 36.11640
	Weight of flask	= 53.92630

Percentage of sugar in blood = 0.044 per cent dextrose.

Dog was then etherized for 2 hours, using 250 cc. of ether, and then bled at end, from left jugular vein.

		gm.
2.	Weight of flask + NaOx + blood	= 93.72710
	Weight of flask + NaOx	= 43.65580
	Weight of blood	= 50.07130

Percentage of sugar in blood = 0.166 per cent dextrose.

Increase in sugar in blood due to anæsthetic = 0.122 per cent dextrose. Urine was positive to Fehling's test.

Remarks.—Here, again, cutting the splanchnic nerves did not remove the effect of ether causing a hyperglycæmia and glycosuria.

A fourth experiment is given in which the animal was operated upon and the splanchnics cut without having first determined the extent of the hyperglycæmia with the splanchnics intact. It is given because it adds to the completeness of the series.

Experiment No. 22.—Dog, No. B 47. Female. Dog was on daily diet of 200 gm. of lean meat. Splanchnics to liver were cut as in previous experiment and after a few days' recovery the ether experiment was begun. Animal was bled from the right jugular vein before beginning of anæsthesia.

gm.

1. Weight of flask + NaOx + blood = 94.13240
   Weight of flask + NaOx = 42.09400

   Weight of blood = 52.03840

Percentage of sugar in blood = 0.0302 per cent dextrose.

Dog was then anæsthetized for 2 hours, using 250 cc. of ether, and bled from the left jugular vein at end.

gm.

2. Weight of flask + NaOx + blood = 86.14350
   Weight of flask + NaOx = 35.23920

   Weight of blood = 50.90430

Percentage of sugar in blood = 0.143 per cent dextrose.

Increase in sugar in blood = 0.0841 per cent dextrose.

Remarks.—This confirms the preceding experiments. The results are put in tabular form for their more ready interpretation.

TABLE No. 4.

SPLANCHNIC NERVE EXPERIMENTS.

Splanchnics to liver.	Dog.	Gender.	Diet.	Anæsthetic.	Percentage of sugar in blood before.	Percentage of sugar in blood after.	Increase in sugar in blood.	Appearance of sugar in urine.	Amount of sugar in urine.
Intact.	B 63	Female.	200 gm. of lean meat daily.	Ether.	0.041%	0.159%	0.118%	+	....
Cut.	B 63	Female.	200 gm. of lean meat daily.	Ether.	0.040%	0.144%	0.104%	+	....
Intact.	B 65	Female.	200 gm. of lean meat daily.	Ether.	0.055%	0.111%	0.056%	+	1.0745 gm. dextrose.
Cut.	B 65	Female.	200 gm. of lean meat daily.	Ether.	0.037%	0.114%	0.077%	+	2.175 gm. dextrose.
Intact.	B 66	Female.	200 gm. of lean meat daily.	Ether.	0.045%	0.094%	0.049%	+	....
Cut.	B 66	Female.	200 gm. of lean meat daily.	Ether.	0.044%	0.166%	0.122%	+	....

These experiments show clearly that the anæsthetic causes its glycosuric effect just as well after the splanchnics to the liver are cut. They further show that with the hepatic artery excluded from the circulation the anæsthetic works its full effect just as well through the portal circulation. This parallels very closely the observations of Whipple and Sperry (17), that chloroform acts just as well and causes the same lesions in the liver when the hepatic artery is excluded from the circulation by ligation.

These results would lead us to think that the anæsthetic acts directly upon the liver, and in some unknown way stimulates that organ to increase the sugar content of the blood. Since the glycosuric effect of ether practically disappears when the liver is excluded from the circulation, we must, it seems reasonable, conclude that the cause of the increased sugar content of the blood lies within this organ, and is not due to any effect upon the muscle or other organ glycogen, or upon the circulating sugar in the blood.

The effect can be brought about by the path of the blood stream, since eliminating the liver from the influence of its glycogenetic fibers does not prevent the occurence of both the hyperglycæmia and glycosuria.

Further investigation is necessary to ascertain whether ether affects the activity of the glycolytic ferments.

Conclusions.

(1) Following the administration of ether to the point of deep anæsthesia, there results, in healthy adult dogs, a well-marked glycosuria.

(2) The reducing body in the urine is dextrose.

(3) The cause of the glycosuria is a definite hyperglycæmia.

(4) The liver is the organ which furnishes the increase in sugar to the blood, as shown by the absence of the occurrence of a hyperglycæmia and glycosuria when the liver is removed from the circulation by an Eck fistula.

(5) Severance of all the splanchnic fibres of the cœliac plexus going to the liver did not remove the hyperglycæmia and glycosuria elicited by ether.

NOTE.—During the time of preparation of this article, Hawk has published two communications, dealing with the subject of post-anæsthetic glycosuria. In one (18) he concludes that this type of glycosuria is due primarily to the effect of ether in stimulating the transformation of glycogen into dextrose. The second (19) paper deals more largely with the rate of urine formation under ether anæsthesia. There occurs an inhibition of the urine-forming function during the time anæsthesia is induced, but such inhibition is quickly followed by a stimulated urine flow which is initialed as soon as the period of anæsthesia terminates. The inhibition of the urine formation was probably due to the effect of ether in constricting the arterioles of the kidney's blood supply.

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THE EFFECT OF OCCLUSION OF THE VARIOUS HEPATIC VESSELS UPON THE LIVER.

By M. C. Winternitz, M. D.,
Associate in Pathology, The Johns Hopkins University.

Although the intrahepatic branches of the hepatic vessels are terminal, their capillary communications are so abundant that, as a rule, embolism or thrombosis of either of them causes no interference with the circulation of the liver. Despite this fact, various pathological changes, varying from simple congestion to true red and white infarcts, characterized by coagulative necrosis in the area supplied by the occluded vessel or vessels, are recognized and have been reproduced experimentally. These will be briefly discussed and a few original cases added.

Occlusion of the Portal Vein.

Occlusion of the portal vein, either thrombotic or embolic, is not rare. This is very evident from Lissauer's report.[1] Among 26,687 cases which came to autopsy at the University of Breslau from 1878-1907, Lissauer found 68 instances of complete or partial thrombotic occlusion of the portal vein or its branches. Most of these occurred as a secondary manifestation in a number of conditions. Portal thrombosis, however, may be primary and is then characterized by a symptom complex of circulatory ileus, as in the case of Lewis and Rosenau.[2] These authors collected 20 other cases from the literature.

As a rule such occlusion has no effect upon the liver parenchyma, since the hepatic artery supplies the blood by the anastomosis between the two systems. That is, while the branches of the portal vein alone supply the acini of the liver with blood and the hepatic artery supplies the interlobular tissue, still the capillaries arising from the hepatic artery empty into the interlobular branches of the portal vein. In this way the hepatic artery, through its anastomosis with the interlobular vein, is capable of compensating when the larger branches of the portal vein are occluded. As long as the small branches of the portal vein are not involved, so long will the hepatic artery be able to nourish the liver parenchyma.

Etiology.—Lissauer concluded, from his analysis of the literature, that slowing of the blood stream is not in itself sufficient to bring about portal thrombosis, that "marantic" thrombi must be exceptionally rare, and that one of the following conditions is essential:

Primary authoctonus atheroma.

Inflammation of the vein wall by extension.

Compression of the vein.

Purulent pylephlebitis.

Lewis and Rosenau, however, conclude from their clinical and experimental studies that bacterial infection plays a very important rôle in portal thrombosis. This is in agreement with the findings of other authors—Welch,[3] etc., in thrombosis elsewhere.

[1] Lissauer: Virchow's Arch., 1908, CXCII, 278.

[2] Lewis and Rosenau: Arch. Int. Med., 1909, III, 233.

Obliteration of the Portal Vein Without Hepatic Changes.

This subject has been reviewed very recently by M. Versé.[4] He cites, as a typical example of fresh thrombosis of the portal vein, a case reported by Saxer in 1902, where thrombi occluded all of the portal radicals. Despite this, the liver was only somewhat small and anemic. The circulation had evidently been carried on by the hepatic artery. Versé then quotes a number of cases of old thromboses of the portal vein.

1. A case of Umber's where the vein was occluded by a thrombus judged to be from 20 to 30 years old. This thrombus was 1 cm. long and just at the hilus of the liver. The liver was relatively small, but otherwise normal. No definite collateral circulation to the liver was determined. The splenic vein also contained a thrombus and the spleen was enormously enlarged.

2. A case described by Heller where the thrombus occluding the portal vein had been extensively canalized. The patient had suffered for many years from a very much enlarged spleen which gradually decreased in size. He died of a ruptured verrucose vein of the stomach. The liver showed no marked changes.

3. A case reported by Risel showed the formation of numerous new veins besides canalization of the thrombus which extended into the hepatic branches. The spleen was much enlarged. Death was caused by a fresh clot in the superior mesenteric vein.

4. A case of Pick's where death followed rupture of a varix of the œsophagus. The portal vein was occluded, and Pick considered that the thrombosis had been secondary to a true hemangioma arising in the wall of the portal vein.[5] An extensive collateral circulation had been established also.

Versé then includes a case of his own where an organized thrombus occupied the splenic and the larger branches of the portal vein. A tremendous collateral circulation had established itself to carry off the portal blood. This was effected through the colic, gastric, œsophageal, omental and left renal, by its communication with the adrenal, veins. The liver received a large amount of portal blood through a mass of cavernous vessels of which the original canalized thrombus

[3] Welch: Tr. Ass. Am. Phys., 1900, XV, 441.

[4] Versé: Beiträge z. path. Anat. u. z. allg. Path., 1910, XLVIII, 520.

[5] Versé discusses the nature of this hemangioma. He does not agree with Pick that this is a true blastoma, but considers it a formation secondary to the thrombosis—as in his case.

formed only a small part. This mass of collateral caverns involved the entire hepato-duodenal ligament.

Experimentally the portal vein has been ligated repeatedly in the production of Eck fistulæ. In several of these cases reported by Whipple[6] the liver, 10 to 11 weeks after ligation of the portal, showed the following picture: "In one dog the fistula between the portal vein and vena cava was quite small (4 x 6 mm.) and the ligature about the portal vein above the fistula was not effective, the opening admitting only the points of the scissors. In the other animal the fistula was quite large and the ligature of the portal vein was efficient.

"The livers were practically the same in both cases. The organ was small, flabby, and rather tough. The lobules were small, presenting a brown, translucent edge and minute central yellow dot. Microscopically there was considerable atrophy and fatty degeneration of the central half of the liver lobule."

In our autopsy reports the following cases of thrombosis of the portal vein without marked hepatic changes have occurred:[7]

1. O. W., white, age 49 years. Autopsy No. 175.

Anatomical Diagnosis.—Carcinoma of the stomach; metastases to the gastro-hepatic glands; *carcinomatous thrombus of the portal vein;* multiple carcinomata of the liver; ascites; hydrothorax (right); emphysema; bronchiectasis; bronchitis; bronchopneumonia with fresh pleurisy.

Liver is very large, covered by tumor masses. The hepatic artery is slightly thickened. The portal vein is of normal size. At its very entrance into the liver there projects into it a large, smooth carcinoma nodule (4 x 2½ cm.). The veins arising in the region of the thrombus are likewise filled with the tumor tissue, and a large mass in the left lobe of the liver is directly continuous with the vein thrombus.

There is in this case no note which would indicate any change in the hepatic tissue resulting from the portal occlusion.

2. A. B., white female, age 59 years. Autopsy No. 214.

Anatomical Diagnosis.—Syphilitic deformity of the liver of extreme degree; chronic passive congestion of spleen with perisplenitis and perihepatitis; chronic thickening of peritoneum, especially around the liver; *recent portal thrombosis;* fat necrosis (slight); acute diffuse peritonitis; chronic diffuse nephritis; mitral insufficiency; hypertrophy of left ventricle; calcification in the wall of splenic vein with parietal thrombus.

The portal vein is very wide, circumference 6½ cm. Just as it enters the liver its lumen is filled with a fresh grayish-red thrombus adherent in places to the intima, but in general easily removed. It extends a short distance into the main branches of the vein and looks very recent in its formation. The vessels in the hepato-duodenal ligament are enveloped in a mass of dense fibrous tissue.

Aside from a marked syphilitic cirrhosis, no lesion was found in the liver. Here again the portal occlusion was without effect. The etiological factor probably was syphilis.

[6] Whipple and Sperry: Johns Hopkins Hosp. Bull., 1909, XX, 278.

[7] The protocols will be abstracted as briefly as possible. Only those parts of particular interest to the subject at hand will be included.

3. F. R., white male, age 37 years. Autopsy No. 262.

Anatomical Diagnosis.—Tuberculous fibrous phthisis—both upper lobes; amyloid infiltration, spleen and kidneys; tuberculous ulceration of large and small intestine; *thrombosis of intrahepatic branches of portal vein.*

Liver.—1250 grams. Surface smooth. Margin round. Lobules visible. Consistency rather increased. Portal vein large, 2 cm. in diameter. Hardened sections of liver show slight increase in connective tissue. Thrombi in portal veins with extensive liver-cell emboli in same vessels. Slight dilatation of the capillaries.

4. L. G. Autopsy No. 462. Dr. Flexner.

Anatomical Diagnosis.—Diffuse suppurative cellulitis of left leg (streptococcus); ascites; chronic adhesive peritonitis; chronic perisplenitis; perihepatitis; *thrombosis of the portal vein;* chronic diffuse nephritis with acute exacerbation; chronic pleuritis, etc.

Liver.—1700 grams, 21 x 15 x 9 cm. It is everywhere adherent. The capsule is thickened, white fibrous-looking and in places reaches 4 mm. in thickness. On section it presents a mottled aspect. The surface is in general cloudy, deep reddish brown in color, with many lighter yellowish areas. Heavy bands of connective tissue proceed in from the porta and the capsule. By this means circumscribed areas of liver tissue are completely marked off. In general the lobules are more distinctly isolated than normally, and the central veins are quite prominent. The consistency of the liver is much increased. In the portal vein are thrombi. The main branch, beginning at the junction of the principal abdominal veins, is almost completely filled by a mixed thrombus which is only slightly adherent. At the entrance into the liver the vein is filled with a more firmly adherent, laminated, somewhat softened thrombus which does not fill the lumen. Some of the principal branches of the portal vein in the liver contain thrombus masses, some of which are recent, scarcely adherent and continuous with the laminated thrombus.

Microscopically there is an increase in connective tissue plus fatty degeneration of the liver cells.

It is quite probable that the mottled appearance of the liver in this case is related to the portal occlusion. The coarse bands of fibrous tissue also suggest a syphilitic cirrhosis.

5. B. S., white female, age 51 years. Autopsy No. 483.

Anatomical Diagnosis.—Carcinoma of the head of the pancreas with extension into the duodenum and stomach; multiple metastases to lymph glands, both adrenals, liver and lung; *thrombosis of portal vein.*

The portal vein is thrombosed just before it enters the liver by a partially decolorized thrombus mass. Aside from the tumor metastases, section of the liver is brownish red in color and homogeneous.

6. L. F., white male, age 45 years. Autopsy No. 567.

Anatomical Diagnosis.—Perforating ulcer of stomach; old adhesive peritonitis around perforation; ulceration into splenic artery and into small pyloric artery; thrombosis of splenic artery; extension of clot into cœliac axis and abdominal aorta; infarction of spleen; *complete thrombosis of splenic vein, with extension of thrombus into portal vein;* thrombosis of many interlobular veins in liver, etc.

Liver is rather small (22½ x 16 x 5 cm.). Surface smooth. Left lobe is adherent to the stomach. On section organ is soft and flabby, but tough. In the right lobe the lobulation is marked. The general color is brownish red. The left lobe is homogeneous in color. The lobules are scarcely visible. In a number, but not in all, of the interlobular veins of the right lobe, there are antemortem clots, reddish and sometimes with white centers. These are continuous with a small thrombus in the portal vein. There are very few thrombi in the interlobular veins

of the left lobe, although they occur, and a small thrombus enters the large portal radical of the left lobe.

Here the thrombus occluding the portal vein had no effect upon the liver parenchyma. No doubt the localized peritonitis was the direct cause of the thrombosis.

7. H. S., white male, age 49 years. Autopsy No. 649.

Anatomical Diagnosis.—Diabetes mellitus; cirrhosis of liver; *thrombosis of portal*, splenic and mesenteric veins; hemorrhagic infarction of intestine; acute peritonitis (serofibrinous, due to gas bacillus); subcutaneous œdema and emphysema, etc.

Liver is firmly bound to the diaphragm over the right lobe. Here the capsule is much thickened (4 mm.) and of cartilaginous appearance. Surface of liver is rough and coarsely granular. On section coarse cirrhosis is visible. The cut surface has a yellow color. Portal vein contains a decolorized thrombus firmly adherent to the wall of the vein, and extending beyond the hilum into some of the main branches.

No definite cause for the thrombus formation in the liver was evident in this case. It is probable that portal stasis referable to the cirrhosis was an important factor.

8. C. H. C., white male, age 58 years. Autopsy No. 850. Dr. Flexner.

Anatomical Diagnosis.—Thrombosis of mesenteric veins; necrosis and gangrene of small intestine; general fibrino-purulent peritonitis; abscess in omentum (operation wound); extension of venous thrombus into portal vein; congestion of liver and spleen.

Liver free from adhesions, weight 2500 grams. On section cloudy, markings distinct owing to moderate congestion. Consistency not increased.

Mesenteric vein is thrombosed. The thrombus in the main branch is partly decolorized, dry and adherent to the vein wall, etc. The thrombus can be traced into the portal and extends into the hilum of the liver. The main branch of the portal vein is apparently completely occluded by the firm, grayish-red mass which is moderately adherent to the vein wall. Beyond the main vein and extending into the left branch, but not into the right, is a recent soft red clot.

Here the occluding mass was a propagative thrombus from the mesenteric vein.

9. Outside Case. Autopsy No. 1398. Dr. MacCallum.

Anatomical Diagnosis.—Primary splenomegaly; *thrombosis of splenic mesenteric and portal veins;* splenic and intestinal infarcts; post mortem gas bacillus invasion.

The *liver* is bound to the diaphragm and surrounding viscera by fibrous adhesions. The portal veins on section are everywhere totally or partly occluded by thrombus masses which are fairly adherent to the vein wall. The liver tissue is much distintegrated by gas formation. The splenic vein is dilated to a diameter of 5 cm. and is distended with an elastic chicken-fat clot which shows points of opacity. This clot can be traced into the portal radicals. It completely occludes the portal vein throughout its length. As the clot approaches the liver it becomes darker. On section it is almost diffluent, especially in the more central part, where it has a purplish-brown color. On the lesser curvature and serous surface of the stomach there are several distended veins which are completely occluded by thrombi, as are also the omental veins.

Microscopically the clot in the mesenteric vein is organized and partly canalized. Surrounding the vein is a sheath of very vascular tissue.

The liver shows microscopically no definite increase in connective tissue. The spleen has a thickened capsule, but the trabeculæ are not much thickened and the connective tissue of the sinuses is much increased.

10. F. S., white male, age 62 years. Autopsy No. 1464. Dr. Marshall.

Anatomical Diagnosis.—Carcinoma of stomach with metastases to liver, etc.; *occlusion of portal vein at hilum of liver by metastases; propagated thrombus in hepatic branches of portal vein, etc.*

Liver weighs 1300 grams, measures 26 x 15 x 6½ cm. Consistency decreased. Surface uneven, due to tumor nodules, etc. On section liver substance is pale, rather opaque and fatty. A tumor nodule is found completely blocking the splenic vein, about 7 cm. from junction of splenic and portal veins. The metastasis extends into the portal, completely occluding it beyond the hilum of the liver. It is firmly attached to the vessel wall, giving it a diameter of 1 to 3 cm. Where this growth ends beyond the hilum of the liver a thrombus begins, extending into the main branches of the portal vein.

11. J. M., white male, age 48 years. Autopsy No. 2706. Dr. Whipple.

Clinical Diagnosis.—Primitive splenomegaly.

Anatomical Diagnosis.—Chronic splenic tumor; sclerosis of splenic and portal veins; cirrhosis of liver and *thrombosis of portal branches;* chronic passive congestion of pancreas and intestine; œsophageal varices with rupture; hemorrhage into the stomach and intestine; anemia; chronic fibroid pulmonary tuberculosis; chronic tuberculous lymphadenitis; miliary tubercles in spleen and liver.

Spleen weighs 1050 grams; measures 21 x 14 x 6½ cm. Splenic vein shows definite sclerosis everywhere, especially marked after one leaves the hilum of the spleen. At the junction of the splenic vein with the mesenteric vein a large thrombus mass is seen tightly adherent to the anterior wall of the mesenteric veins, but only partly occluding its lumen. Thrombus is of a gray color showing definite ridges and furrows on its surface. The portal vein, however, is completely occluded by a firm thrombus mass which shows some fresh central blood clot, but is mostly made up of gray translucent tissue. As one goes upward, one finds the two branches of the portal vein completely obliterated by similarly appearing thrombus masses. These thrombi show fibrous translucent tissue at the margin, merging into the vessel wall, while the central portions show a greater or lesser degree of brownish-red blood clot, or even fluid blood. Some of these vessels seem to show small channels full of fluid blood, in the organized fibrous thrombus mass.

Liver weighs 1200 grams; measures 22 x 16 x 7 cm. Its upper surface, as a rule, is pretty smooth and of a pale brown color. Near its anterior margins it shows considerable granulation of its surface, prominent nodules of opaque tissue alternating with depressed areas in which are dilated blood vessels. The lower surface of the liver has a more marked granular appearance, especially around the fissure at the entrance of the portal structures. Cut surface in the upper portion shows great anemia, but little increase in connective tissue. As one approaches the transverse fissure, however, the connective tissue becomes considerable in amount; embedded in it are irregular nodules of opaque yellow appearance, apparently hypertrophied islands of liver tissue. This connective tissue increase seems localized pretty sharply around the branches of the portal vein and becomes progressively greater in amount as we approach the larger thrombosed branches of the portal vein.

The *œsophagus*, opened up from behind, shows tremendous distention of the veins underneath its mucosa. These veins are very tortuous; some of them, dilated to a diameter of 3 mm., form little miliary saccular aneurysms which bulge very definitely from the walls of the dilated venules. Some show superficial necrosis of the mucosa covering them and are seemingly just on the point of

rupturing. Twelve cm. above the cardiac junction is a small erosion 3 x 1 mm. with clean edges, communicating directly with the lumen of the large dilated veins, into which a good-sized probe can be passed with ease. Blood can be squeezed through this opening. The stomach contains 650 cc. of dark jelly-like blood clot. Its mucosa is intact everywhere. Just around the cardiac orifice it shows a network of large tortuous dilated veins, which, however, only persist for a distance of 5 cm. from the junction with the œsophagus. The duodenum is normal. Dissection of the dilated veins around the cardiac orifice shows them to communicate with branches of the splenic vein given off 3 or 4 cm. from the origin of the vein at the hilum of the spleen. A few of the smaller veins in this position seem to anastomose with the veins along the lesser curvature of the stomach.

The *liver* shows an increase in connective tissue between the lobules. This, however, is not uniform, being most marked in sections taken from the region of the transverse fissure. The connective tissue is sharply confined to the margins of the lobules and does not extend into the central portion, except where the lobule has undergone complete degeneration. The portal vein shows a thrombus made up of old fibrous tissue into which numerous capillaries have grown. Some of these have become enlarged to a considerable size and contain fresh blood. The bile ducts in this neighborhood show signs of active proliferation.*

The above report of Autopsy No. 2706 has been given in greater detail because the findings do not correspond with the clinical diagnosis of primitive splenomegaly.

These 11 cases do not present any new features. In all, the portal vein and its radicals alone were involved. In all, the finest interlobular veins were free. In all, the general circulation was maintained to a sufficient extent to prevent any striking changes in the liver directly attributable to the occlusion. In 3, the thrombi were the direct result of tumor invasion; in 2, they were the result of a localized peritonitis (one of these was possibly a syphilitic process); in 1, they accompanied a syphilitic liver; in 2, they were secondary to cirrhosis; in 1, they were a direct extension from a thrombosed mesenteric vein; in 1, a secondary process occurring in the course of a general tuberculosis, where there was amyloidosis; and in 1, the process seemed primary.

It is interesting to compare the findings in the above cases with the much more extensive series of Lissauer. In his series, 6 of the 68 cases of thrombosis of the portal vein were associated with atrophic cirrhosis of the liver; in 7, with syphilis of the liver; in 2, with primary carcinoma of the liver; in 7, with carcinoma of the stomach, accompanied by metastatic growths in the liver; in 2, with secondary carcinoma of the liver; in 6, with primary carcinoma of the biliary passages; in 9, with gall-stones and inflammatory lesions of the gall-bladder; in 10, with diseases of the pancreas; in 1, with suppurative inflammation of the umbilical vein; in 6, with diseases of the spleen; in 6, with gangrenous appendicitis; in 2, with carcinoma of the intestine; in 1, with a pelvic abscess; and in 1, with no definite cause.[8]

* There are two other cases of portal thrombosis in our first 3500 autopsies: one autopsy, No. 224, where there was only a small parietal thrombus of the portal vein, and autopsy No. 1409, where the picture in the liver was so obscured by complicating conditions that the result of the portal occlusion upon the hepatic parenchyma was indefinite.

[8] Quoted by Lewis and Rosenau.

Two cases, Nos. 9 and 11 of our series, deserve a word of comment. Versé points out that the tremendous enlargement of the spleen, the anemia which so often occurs, and the integrity of the liver may often suggest the clinical picture of Banti's disease. Very great enlargement of the spleen may result from simple vascular changes accompanying portal thrombosis; and he concludes that only then may we speak of a primary splenomegaly, when absolutely every other organic cause has been excluded. The above cases are not instances of primary splenomegaly, since the extensive thrombosis is quite enough to explain the findings.

It is essential to remember portal thrombosis in the differential diagnosis of splenomegaly.

Embolic or Thrombotic Areas of Congestion.

Despite the extensive anastomosis between the branches of the portal vein and the hepatic artery, in rare instances and under accessory circumstances a condition somewhat resembling the macroscopic picture of hemorrhagic infarction, and often spoken of as the "atrophic red infarct of Zahn," may follow plugging of branches of the portal vein. The "atrophic red infarcts of Zahn" are triangular, rectangular or irregularly wedge-shaped areas with their apices at the occluded vessel. As a rule they are dark red or reddish-brown, but pale areas have also been observed. Microscopically there is simply a congestion of the intralobular capillaries with slight atrophy of the liver cells and possibly some pigmentation. It is of importance to note that necrosis does not occur in these areas. Ruczynski[9] explains their production in the following way. The blood from the portal vein no longer flows into the hepatic vein and the latter is only poorly filled by the blood of the hepatic artery. As a result there is a stasis in the hepatic vein due to the deficient *vis a tergo,* and the picture of a congested liver with dilatation of the central veins and capillaries and atrophy of the liver columns is gradually produced. This is the condition which was described by Zahn.[10] Orth[11] had described it previously and in his text-book expresses clearly that they are the result of an aseptic embolic or thrombotic process. He calls them areas of circumscribed congestion, atrophy or cyanotic atrophy which may be viewed as a type of hemorrhagic infarction but never as a complete infarct.

Many observers have described this picture. Bertog[12] described two cases in which a "chronic red atrophy" of the liver was the result of decreased portal blood supply from compression of portal roots by chronic peritonitis. He considered that any hindrance to the free flow of portal blood to the liver might produce an atrophy of the liver similar to what occurs in a liver of congestion. Cohnheim and Litten[13] described a "nutmeg" liver involving the part of the gland

[9] Ruczynski: Ztschr. f. Heilk., 1905, XXVI, 147.

[10] Zahn: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte 1897. Leipz. 1898, Part 2, p. 9; or Centralbl. f. allg. Path., 1897, VIII, p. 860.

[11] Orth: Lehrbuch der Path. Anatomie, 1887, I, 917.

[12] Bertog: Greifswalder Beiträge, 1863. Quoted by Chiari.

[13] Cohnheim and Litten: Virchow's Archiv., 1876, LXVII, 153.

supplied by an occluded portal radical. Klebs [14] cited the presence of wedge-shaped areas after occlusion of radicals of the portal vein; these areas showed microscopically only a granular degeneration. Wagner [15] described an instance of narrowing and thrombosis of several portal radicals resulting in deep red or pale wedge-shaped areas. Köhler [16] reported three cases of cyanotic atrophy after occlusion of large portal radicals. His first case concerned a man who, 7 days before death, underwent an operation, *i. e.,* excision of rectum for carcinoma. At autopsy one of the portal veins contained an antemortem clot and the liver supplied by the branch showed the usual picture macroscopically. Sections showed less fat in the atrophied cells and an increase of brown pigment. The second case was one of malignant tumor of the peritoneum with thrombosis of a portal radical and the nsual picture of pseudo infarction. In the third case there was a septic embolus in the right branch of the portal vein, and a large hyperemic wedge-shaped area of liver containing multiple small abscesses corresponded to the distribution of the occluded vein. The thrombus arose in the splenic vein. Köhler concluded that not only portal thrombosis, but also weakened heart action was essential to obtain the above picture of congestion. He considered the atrophy of the liver cells to result from pressure of the dilated capillaries and inactivity of the liver cells. Pitt [17] added three more cases. The first concerned an individual who died 5 days after an operation for relief of an incarcerated scrotal hernia. The liver showed an atrophic zone 2 inches in diameter and the corresponding vein was occluded. Sections only showed dilatation of the capillaries. His second case, an old man who died of cerebral hemorrhage, showed corresponding to many thrombosed branches of the portal vein, numerous sharply demarcated pale or dark areas with dilatation of the capillaries in the latter. In the third case there was a pale area of liver, the result of embolic plugging of a portal branch following operation for ovariotomy. Ruczynski [18] explained the pale areas of the third and second cases by the persistence of anemia following the portal occlusion. Chiari [19] in a very comprehensive report published in 1898 collected most of the above cases and added 17 cases observed by him from 1877 to 1898. On account of the large number of personal observations he is inclined to consider this condition not at all uncommon. Of his 17 cases, 15 resulted from emboli arising in branches of the portal vein. These he subdivided into those cases where the thrombosis of the portal roots followed by hepatic emboli occurred without any external influence (7 cases) and those where some operative procedure involving the portal roots occurred shortly before death—(8 cases). The two remaining cases resulted from thrombi arising within the intra-hepatic radicals of the portal vein.

Of the group of emboli occurring without external cause, 4 were carcinomatous in nature, 1 occurred in a case of "marasmus," 1 in typhoid ulcerative enteritis and 1 originated from a thrombus formed in the splenic vein, the result of pressure from an aneurysm of the splenic artery. In several cases of the second group the thrombi in the roots of the portal vein were the direct result of ligatures applied to these branches at the time of operation.

Chiari considered the dark areas of the liver to be a purely mechanical result following occlusion of the large branches of the portal vein, namely, local areas of congestion involving primarily the central vein and the neighboring capillaries of the central portion of the lobule with atrophy of the liver cells. The smallest branches of the portal vein in the affected areas of the liver were free of obstruction. Similarly the central veins and the hepatic arteries in these areas were uninvolved. Blood extravasation only occurred twice and then only in small amounts. Necrosis of the liver cells was never found. Chiari's findings confirmed the observations of other authors concerning the origin of these areas, *i. e.,* that they were only circumscribed areas of congestion. The liver cells received enough fresh blood through the inner portal roots to exist. The *vis a tergo,* however, was not sufficient to keep up the normal circulation, and as a result there was a reflux congestion of the blood from the right auricle which, together with the constantly decreasing nourishment of the liver cells, caused them to atrophy. It was worthy of note that in a number of cases the liver cells of the affected zone, were practically fat free, while in the remaining liver the fat was present in considerable amounts. This Chiari explained by the stoppage of the flow of the portal blood through the area. Finally Chiari concluded with Köhler that simple occlusion of branches of the portal vein was not sufficient to bring about the formation of the so-called atrophic red infarct. There must be added to the occlusion one of the following conditions:

a. Weakening of the arterial current to the liver.
b. Venous congestion.
c. A combination of the two above conditions, or
d. Impaired cardiac action.

This latter he considered to be the most important.

Ruczynski adds several more cases.

That of Lazarus Barlow, concerned a young man, who had been crushed between the buffers of two railroad cars. Death followed in three days. At autopsy there was a large tear in the right lobe of the liver. In the center of this tear was a thrombosed portal vein and corresponding to the distribution of this vessel was a large wedge or grayish-white tissue. Lazarus Barlow considered this an anemic infarct, but Ruczynski disagreed with this diagnosis since the author does not mention in his microscopical findings the presence of necrotic liver cells.

Longcope reports a case where, besides numerous metastatic cancer nodules from a primary gastric growth, there was a deep red triangular area whose base measured 3 cm. The portal vein leading to this discolored zone was occluded.

Finally, Versé [20] reports a case where in a young woman

[14] Klebs: Handbuch der Path. Anatomie, 1896, I.
[15] Wagner: Arch. f. klin. Med., 1884, XXXIV, 520.
[16] Köhler: Arb. a. d. path. Institut in Göttingen, 1893, 121.
[17] Pitt: Tr. Path. Soc. Lond., 1895, XLVI, 74.
[18] Ruczynski: *Loc. cit.*
[19] Chiari: Ztschr. f. Heilk. 1898, XIX, 475.
[20] Versé: Verhandl. d. deutsch. path. Gesellsch., 1909, XIII, 314.

with periarteritis nodosa, large, circumscribed, depressed areas of congestion followed occlusion of small portal veins.

Zahn[21] studied the effect of injection of sterile mercury into the mesenteric veins of dogs. After eight days, the shortest period, there were red, triangular areas in the liver which were typical of the atrophic red infaret in 35 days. They showed microscopically the picture of congestion and atrophy of the hepatic parenchyma, but there was no necrosis.

The following three cases belong to this group of liver changes following occlusion of the portal vein radicals.

The first case is so unique that a rather detailed account will be given.

W. K., white male, age 40 years. Admitted to the medical clinic of the Johns Hopkins Hospital, January 5, 1911, complaining of stomach trouble. Previous to present illness, history was negative. P. I. began 5 months before admission, with sudden, acute abdominal pain and vomiting. This was first blackish and gradually became paler. The vomiting persisted and there was loss of weight, amounting to 100 pounds. Examination revealed nothing of importance except a HCl deficit of 10, and a total acidity of 8; and an increased resistance in left epigastrium. The Wassermann reaction was negative. Occult blood was repeatedly demonstrated in the stools. On March 20, an exploratory laparotomy was performed by Dr. Finney. The stomach was found greatly dilated. Its walls were atonic, but there was no evidence of new growth.

The duodenum was greatly enlarged and relaxed, being almost twice its normal diameter, with soft, flabby walls. Aside from some dense adhesions, some of which were severed, nothing of importance was observed. The patient did not recover from the operation.

Died, 8 p. m., March 21, 1911.

Autopsy, 10 p. m., March 21, 1911. Autopsy No. 3519. Dr. Winternitz.

Anatomical Diagnosis.—Chronic inflammatory stricture of the jejunum, probably following strangulation of the bowel after a volvulus; multiple thrombi in the mesenteric vessels; dilatation of stomach and duodenum; extensive scarring and atrophy of wall of jejunum; chronic adhesive peritonitis, particularly marked about the region of the stricture; chronic mesenteric lymphadenitis; pressure of inflammatory mass on retroperitoneal tissues, resulting in thrombosis of left renal vein; slight atrophy of left kidney; (exploratory laparotomy); dislodgment of portion of thrombus in renal vein; embolus into one of the smaller radicals of the pulmonary artery with hemorrhagic infarction of lung. *Dislodgement of mesenteric thrombus; embolism into large right portal vein with formation of a localized area of congestion in the liver.*

Abdominal cavity. The adhesions are chiefly in the left hypochondrium. The omentum is bound tightly to the pancreas and this with the duodenum and spleen forms one compact mass, over which the jejunum passes emerging from a small knot of adhesion.

Liver measures 28 x 20 x 9½ cm. Its surface is smooth. On section it presents an extremely striking picture. A large area in the right lobe has a much deeper brown color than the remaining liver tissue. This area is irregularly wedge-shaped extending to the hilus of the gland where the apex of the triangle is found. Throughout this darker portion of the liver the portal vein radicals are occluded by large ante mortem clots which are quite friable. These converge to one large hilic branch of the portal vein where a large non-adherent clot is found. The two areas of liver, namely, the darker area in which the portal vessels are occluded and the surrounding paler brown areas present otherwise only minor differences. In both zones the lobules are distinct. In the darker portion they are somewhat smaller.

[21] Zahn: *Loc. cit.*

Microscopically, in the area involved by the occluded portal radical, the liver cells stain paler; the columns are somewhat thinner, the vessels slightly dilated. The change is so slight that it might not be noted were one's attention not specially directed towards it. Neither the interlobular veins, hepatic arteries nor the central veins are involved by thrombus.

This case represents a typical example of the result of embolism of a large portal radical. The embolus arose from a thrombus in the mesenteric vein which was probably dislodged at the time of operation. The area of pseudo infarction in the liver is consequently very young, probably less than 24 hours.

13. R. F., white male, age 40 years. Autopsy No. 1691. Dr. Opie.

Anatomical Diagnosis.—Cholelithiasis; calculus impacted in diverticulum of Vater only partly filling it and occluding its duodenal orifice; acute hemorrhagic pancreatitis; disseminated abdominal fat necrosis; partial thrombosis of splenic vein; *embolism and thrombosis of portal vein.*

Liver weighs 1350 grams. Surface is smooth. Upon the upper surface of the right lobe are three irregular, very slightly depressed areas conspicuous from the fact that they are of a dull red color while the remainder of the surface is yellowish. The cut surface has a bright yellow color. The periphery of the lobules are golden yellow, the central part reddish, corresponding to the areas mentioned on the surface, on section; the tissue below has a similar appearance, the corresponding area being narrower as the surface becomes distant (*i. e.* irregularly wedge-shaped). Here this tissue is of a dull red color. Within such areas are seen sections of veins plugged, and distended with red thrombus. These are found to be portal veins. The vein in one of these areas has a diameter of about 4 mm. It is plugged with a red thrombus, which stops abruptly at the apex of the wedge, where it ends in a yellowish-white embolus. In addition to these large areas mentioned, several distinctly wedge-shaped smaller ones are present. The large portal branches are normal.

Microscopically. Within the lobules, usually at a distance from the portal spaces, are areas where the liver cells are clear and unstained with eosin in contrast to those about. With the high power the protoplasm is entirely unstained, but is slightly granular. The cell body is somewhat swollen. The nucleus is smaller, somewhat irregular, and no longer vesicular, staining homogeneously. In the center of one of these areas, a group of 10 to 12 cells whose protoplasm takes a conspicuous deep eosin stain is found. The nuclei are preserved; many polymorphonuclear leucocytes occur between these cells. (This case was reported by Opie in the JOHNS HOPKINS HOSPITAL BULLETIN, 1901, under the title, "The Etiology of Acute Hemorrhagic Pancreatitis").

14. B. V., 1908-9, D. W. Died, February 19, 1908, 2.15 p. m. Autopsy, February 20, 1908, 11.30 a. m. Dr. Meloy.

Anatomical Diagnosis.—Infected ovarian cyst; multiple miliary abscesses (operation); acute and chronic peritonitis; chronic diffuse nephritis (large white kidney); infarct of spleen, *zone of congestion of liver corresponding to distribution of occluded portal vein by thrombus;* amyloidosis; chronic perihepatitis and perisplenitis; anemia; emaciation; polypoid œdematous tumors of bladder.

Unfortunately no other data concerning this case was available. At the time of autopsy, however, the liver was practically identical in appearance with that of Case 12. Microscopically, too, there was no evident change in the organ. It is probable that here also there were thrombi in the portal roots which only reached the intrahepatic branch after operation.

To briefly summarize, obstruction of the large branches of the portal vein may cause irregular wedge-shaped areas of congestion, and in rare instances of anemia, in the liver. These are not true infarcts since they show microscopically only a dilatation of the central veins and intralobular capillaries, together with atrophy of the liver cells and no necrosis. Such an area may shrink considerably. This shrinkage is due to atrophy of the liver parenchyma, but to what extent pressure of the dilated capillaries, decreased nutrition, actual necrosis, or inactivity of the cells affects this atrophy is a problem inseparably associated with the still unsettled question of the atrophy of the liver occurring in chronic passive congestion due to general causes.

In all these cases the smallest branches of the portal vein in the congested zones were free of obstruction. The hepatic vein and artery were always unobstructed. The blood reached these zones through the inner portal vein radicals, but not in sufficient quantity to keep up the normal flow. This allowed a reflux from the larger hepatic vein which resulted in congestion. It must be repeated that occlusion of the portal vein alone may not necessarily be followed by congestion in zones supplied by the occluded vein. In order that these results should follow Köhler and Chiari consider that accessory circumstances must exist, such as venous congestion, decreased cardiac activity, etc. The ultimate result of these areas of congestion is not known and the shortest time in any of the cases reported in which the area of congestion occurred following the thrombosis of the portal vein was three days in a case reported by Chiari. In Case 12 the time was less than 24 hours.

True Anemic or Hemorrhagic Infarcts of the Liver Resulting from Occlusion of Smallest Interlobular Branches of the Portal Vein.

True infarcts of the liver with necrosis occur as the result of occlusion of the smallest portal vein radicals, namely, the interlobular veins. Under these conditions the blood from the hepatic artery no longer can reach the capillaries of the lobule by its anastomosis with the interlobular veins. There is then a complete mechanical deficiency of the circulation leading often to complete local necrosis of the liver parenchyma which may be combined with hemorrhage.

Cohnheim and Litten [22] emphasized the fact that if the liver parenchyma is to remain free of secondary changes, the interlobular vein must not be involved by the occluding mass. Orth [23] also said that while there may be no effect from occlusion of big branches of the portal vein, if the interlobular branch is involved atrophy as well as necrosis results. To this type of necrosis belong the well-known necrosis of eclampsia as described by Schmorrl, Klebs, Lubarsch, etc. Chiari [24] in his discussion of these infarcts includes cases described by Rattone and Mondino, and Osler. Rattone and Mondino deny the occurrence of inner portal vein radicals, and consider the entrance of the branches of the hepatic artery into the capillaries of the acini of the greatest importance. They describe two cases of infarction. In their second case the hepatic artery and portal vein were both occluded in the affected zone. This was also true in Osler's case. The liver was cirrhotic and showed a reddish-brown necrotic area on the surface which extended through the liver tissue as a triangle. The portal vein leading to this was thrombosed and Osler considered the cirrhosis to have shut off the hepatic circulation.

Chiari then adds three cases. The first occurred in a case of tuberculosis. The liver was the seat of multiple small tuberculous nodules. There were numerous thrombi in the mesenteric veins leading from the colon. Microscopically aside from the tuberculosis there were numerous interlobular veins plugged by emboli, from the mesenteric thrombi. There were also small areas of coagulative necrosis of the liver cells which Chiari considered to be infarcts. The case is not convincing.

In his second case following an operation (resection of the pylorus of the stomach) there were thrombi in the gastric and pancreatic veins. These fed small emboli to the interlobular portal branches and multiple small whitish infarcts characterized by typical coagulative necrosis resulted.

As an instance of infarction of the liver resulting from thrombosis of the interlobular veins he cites a case of eclampsia.

Ruczynski [25] adds two more cases of this type. Castigne's case in which necrotic areas occurred in the liver the result of small emboli from thrombi in the portal roots and Longcope's case where there were yellow thrombi in the hepatic vein and smallest portal veins causing yellow, necrotic infarcts in the parts supplied by the portal vessel.

Versé also describes a case of chronic perityphilitis in which the surface of the liver showed numerous pale, brown, depressed areas. On section these were dark red, soft and spongy and showed microscopically dilated vessels and necrotic liver cells. The portal vein was occluded by an old thrombus 5 cm. from the hilus, and near the infarct was a canalized fibrous thrombus. This case is of further interest since the thrombosis of the large portal root was without effect, but occlusion of the small branches brought about necrosis. The following case belongs to this group:

15. G. L., colored male, 53 years. Autopsy No. 228.

Anatomical Diagnosis.—Primary carcinoma of stomach; secondary in liver, lymph glands and pleura; chronic diffuse nephritis; nodular arteriosclerosis; *thrombosis of minute portal vessels; softened hemorrhagic infarcts of liver.*

Liver weighs 2600 grams. It is very large and contains numerous rather soft, nodular masses which vary considerably in size ½ to 7 cm. These masses project slightly above the surface and are flat and sometimes very slightly umbilicated. Some of the nodules are exceedingly soft. On section a large amount of bloody fluid escapes. This appears to come from smooth walled cavities. Some of these cavities are situated directly in the liver tissue while others are surrounded by a small amount of the tissue of the tumor. These spaces sometimes form large con-

[22] Cohnheim and Litten: *Loc. cit.*

[23] Orth: *Loc. cit.*

[24] Chiari: *Loc. cit.*

[25] Ruczynski: *Loc. cit.*

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necting cavities in the liver. Some of these are filled with pure cells. In some of the larger ones thrombi are seen projecting into the cavities from minute branches of the portal vein. On further examination of these spaces in the liver they nearly all seem to be in relation to the tumors often running on one side of these. Some of the cavities are round, others very irregular, divided by numerous septa. Often the larger ones communicate. Branches of both the portal and hepatic veins especially the latter can be traced into them. On scraping the walls no epithelium was found.

An instance of peripheral zonal necrosis, similar to that occurring in eclampsia, was found in an adult male in our autopsy series. This is of interest because peripheral zonal necrosis is considered by some to be the characteristic anatomical picture of eclampsia.

Occlusion of the Hepatic Artery.

The anatomy of the hepatic artery is such that firstly on account of its position at its origin from the cœliac axis it is little disposed to emboli and secondly on account of the free anastomosis of its hepatic branches with the neighboring vessels—inferior phrenic, internal mammary, superior adrenal, and the arc of vessels on the lesser curvature of the stomach—occlusion of its branches is usually without effect.

Experimental ligation of the hepatic artery varies in its results according to the animal which is used. In rabbits necroses usually result, while in dogs there is very little effect aside from a possible slight atrophy of the liver cells in the center of the lobule (Cohnheim, Litten, Whipple, etc.).

Tischner ligated the hepatic artery in 26 rabbits and in only one was there no necrosis. He says that the occlusion of the hepatic artery which is supposed only to nourish Glisson's capsule causes degeneration of the walls of the portal vein which leads to thrombosis and infarct formation. In man anemic infarcts resulting from occlusion of branches of the hepatic artery are extremely rare. To this type of infarction belong a number of cases cited by Chiari; namely, those of Obermuller, Orth, Ogle, Kaufmann, two original contributions of Chiari's, and two by Ruczynski who also cites cases by Baldwin, Heile and Bonome. Ruczynski's second case is particularly interesting for here despite thrombosis of both the hepatic artery and portal vein, the process had been so gradual that no infarct, but only a local congestion with atrophy of the liver cells resulted.

Chiari emphasized the difference between these infarcts and those resulting from occlusion of the smallest portal vein radicals. In the arterial infarct there is also necrosis of the blood vessels and connective tissue which are nourished by the hepatic artery. There are no cases of this type in our first 3500 autopsies.

Occlusion of Hepatic Vein.

Welch [26] cites a case reported by Arnold where a condition similar to the "atrophic red infarct of Zahn" followed plugging of an hepatic vein by a retrograde embolus.

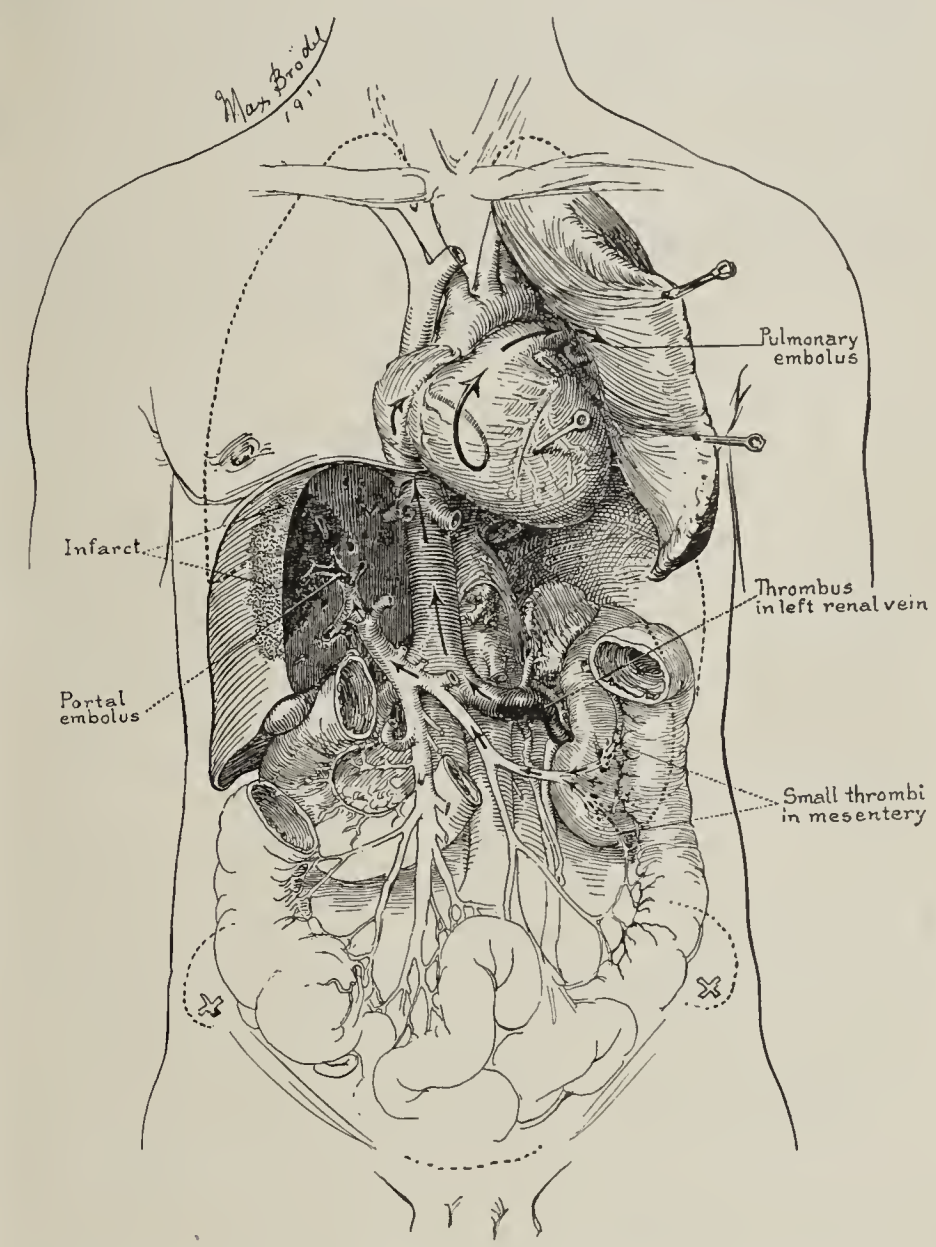
[26] Welch: Thrombosis and Embolism; Allbutt: System of Medicine, 1899, VII, 280.

In some unfinished experiments B. Bernheim and myself have almost completely ligated an hepatic vein of a dog without marked effect. The lobe of the liver a few weeks after ligation is indistinguishable from the remainder of the organ macroscopically or microscopically. This is confirmed in the following post mortem record:

F. E., white male. Autopsy No. 769. Dr. Flexner.

Anatomical Diagnosis.—Amœbic dysentery; amœbic abscess of liver penetrating into lung. Fibrino-purulent pleurisy; perforation into inferior vena cava. *Thrombosis of inferior vena cava extending into right auricle and hepatic veins.*

The inferior vena cava beginning at a point just above the rupture (of liver, abscess into cava), contains an occluding de-



colorized, firm, adherent thrombus, which extends upwards and projects into the right auricle which it about one-third fills. Some of the hepatic veins are thrombosed in part of their extent. The thrombi in the upper part are decolorized, but deeper in the liver tissue they are red and soft.

Conclusions.

1. On account of the extensive anastomosis of the intrahepatic branches of the portal vein and the hepatic artery, occlusion of either of them is usually without effect upon the liver parenchyma.

2. The portal vein may be completely occluded and the liver only appear slightly smaller and congested. In these cases an extensive collateral circulation usually establishes itself in the hepato-duodenal ligament and the portal blood is in this way carried to the interlobular vessels.

3. Following occlusion of the portal vein the entire liver, if it is the main branch, or only the part supplied by the occluded vein may present a much more congested appearance. This is due to the insufficiency of arterial anastomosis which is enough to nourish the liver cells and prevent necrosis, but which allows the blood from the systemic veins to dam back into the liver capillaries. This picture is only produced when the general circulation is impaired.

4. When the smaller interlobular branches of the portal vein are occluded the anastomosis with the hepatic artery becomes ineffectual and there is a total mechanical obstruction of the circulation in the area. This is followed by infarct formation. There is necrosis of the liver cells often accompanied by hemorrhage. The necrosis of eclampsia belongs to this group.

5. Occlusion of branches of the hepatic artery may result in true infarct formation. This is rare, firstly, on account of its peculiar position at the cœliac axis, and secondly because of its abundant anastomoses.

6. Occlusion of both the portal vein and the hepatic artery results in infarct formation unless the process is very gradual.

7. Occlusion of the hepatic vein may bring about a congestion in the zone drained by it or may be absolutely without effect.

The accompanying illustrations, kindly made by Prof. M. Brödel, illustrate very well the course of the various emboli in Case 12, and secondly the resultant wedge-shaped area of congestion following the localization of the embolus in one of the large right branches of the portal vein.

THE TEACHING OF EXPERIMENTAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY TO LARGE CLASSES.*

By Richard M. Pearce, M. D.,

Professor of Research Medicine and of Pathology, University of Pennsylvania.

The course in experimental pathology and pathological physiology here presented in outline, is an attempt to bring physiology into relation with morphology and symptomatology and thus to fill the gap which exists between the autopsy room and the laboratory of pathological histology on the one hand and the clinic on the other. Many teachers of pathology, following the lead of Cohnheim, have, it is true, introduced into their class work demonstrations illustrating some of the important problems of pathological physiology; but these have usually been perfunctory demonstrations given in a fragmentary way before the entire class, and without, as a rule, the utilization of the methods of exact registration employed in physiology. Of an entirely different character is the method which was followed for several years by Dr. W. G. MacCallum at the Johns Hopkins Medical School and is continued there along similar lines by Dr. Whipple. In this course a class of eight students worked for a period of two to three months on one organ or a group of related organs, utilizing all the methods which experimental pathology could bring to bear on the problems under consideration. The value of such a course cannot be over estimated and it should have, as an elective, a place in the curriculum of every good medical school. It has, however, the disadvantage that it cannot be given, on account of the great detail of the work, to all the members of a large class and must remain essentially an elective course combining instruction and research for a small number of students.

For a long time, it has seemed to me desirable that a course in experimental pathology should be developed which, while including as far as possible valuable features of MacCallum's "small group" course, should at the same time be so arranged as to be available to all the members of a large class. Amphitheatre demonstrations are not advisable, as only the few men close to the demonstration table benefit by such procedures. Likewise individual work by the student, such as is now given in our better courses in experimental pharmacology, is out of the question, for the present at least, on account of the lack of equipment and space in most of our laboratories of pathology. The course which I have given during the latter half of the past academic year has been a compromise between these two methods, in that, although the demonstration method has been used, the number of demonstrations in one period has been sufficient to break up the class into small groups. Thus a class of 90 men has been divided into two sections, each section meeting, during 14 weeks, once a week for one hour. At these sessions at least five demonstrations, each under the direction of a member of the department, have been presented simultaneously. Thus each section of 45 men was subdivided into five groups of 9 men, and each of these had at least 12 minutes for a demonstration. The room in which the course was given was of a size sufficient to allow a wide space between the demonstration tables, and also to allow the passage of groups from table to table, on signal, without confusion.

The general scope of the course was based in part on Cohnheim's classical experiments, MacCallum's course at Hopkins, Rous' course at Michigan, Longcope's elective course in "medical correlation" given last year at this school and the demonstration courses to physicians given for several years in the Medical Department of Columbia University, and in part on an extensive personal acquaintance with the methods of experimental pathology and their possibilities. The course is not to be considered as complete or perfect, or as in every way ideal, but rather as a tentative summary of what has, in my hands, proved most satisfactory in the instruction of large classes. The possibilities of enlarging its

* Read before the International Association of Medical Museums, Chicago, April 13, 1911.

scope and of improving its presentation are numerous and will be evident to any one familiar with the methods of physiology and chemistry as applied to experimental pathology.

The following outline is a copy of the mimeographed sheets given each member of the class two days before the demonstrations:

EXERCISE I.

BLOOD DESTRUCTION AND JAUNDICE.

Table I. (a) Rabbit which received, three days before demonstration, 0.001 gm. rattlesnake venom in ear vein. Note *hemoglobinuria*, the result of the hemolytic action of snake venom.

(b) Dog which received, three days before demonstration, 0.2 cc. of hemolytic immune serum per kilo of body weight in saphenous vein. Note *hemoglobinuria* (and jaundice ?).

Table II. Experiments *in vitro* explaining phenomena seen above *in vivo* (hemagglutination and hemolysis).

Table III. (a) Rabbit which received, 24 hours before demonstration, 0.001 gm. cantharidin in acetic ether, subcutaneously. Result: *Free blood in urine* (hematuria), *not hemoglobinuria*—equivalent to a hemorrhagic nephritis.

(b) Microscopic preparations showing the sediment of the urine of (1) *hematuria* (red blood corpuscles present) and (2) *hemoglobinuria*.

Table IV. (a) Dog with *jaundice*. the result of the ligation of the common bile duct for three days. Note skin, conjunctiva and urine.

(b) Tests for bile in urine of Ib and IVa.

Table V. (a) Test for albumin in urine of Ia, Ib, IIIa, IVa.

(b) Spectroscopic test of urine of Ib.

(c) Microscopic sections illustrating the changes in the various organs of the above animals.

EXERCISE II.

DEGENERATION AND NECROSIS.

Table I. (a) Rabbit: Gross demonstration of *cloudy swelling* due to repeated injections of cantharidin in ether.

(b) Microscopic preparations of liver and kidney treated with salt solution and acetic acid.

Table II. (a) Rabbit: *Fatty changes* due to poisoning by phosphorus.

(b) Microscopic preparations treated by acetic acid, Sudan III and osmic acid.

Table III. (a) Dog: *Necrosis* from loss of blood supply. Ligation of superior mesenteric artery and one branch of renal artery.

(b) *Gangrene* in guinea pig's leg secondary to ligation of femoral artery and vein.

Table IV. (a) Rabbit: Illustrating gas formation in *emphysematous gangrene*. Injection of *B. aerogenes capsulatus* in ear vein; animal then killed and placed in thermostat at 37.5° C. for 24 hours.

(b) Microscope with preparation of *B. aerogenes capsulatus*.

Table V. (a) Guinea pigs showing *caseation* of tuberculosis. Four weeks after injection of bovine tubercle bacilli into peritoneal cavity.

(b) Microscope with preparation of *B. tuberculosis*.

EXERCISE III.

INFLAMMATION AND REPAIR.

Table I. (a) Ear of rabbit exposed to water at 56° C. for three minutes—condition after 24 hours.

(b) Ear of rabbit 24 hours after rubbing with croton oil.

(c) Microscopic preparations illustrating histology of each.

Table II. (a) Rabbit: *Pleuritis* due to injection of aleuronat. 48-hour lesion.

(b) Ditto due to injection of turpentine, 48-hour lesion.

(c), (d) } Microscopes with exudate from { (a), (b)

Table III. (a) Rabbit: Multiple *embolic abscesses* resulting from injection of staphylococcus pyogenes aureus in ear vein. 48-hour lesion.

(b) Microscopic preparations illustrating lesion in kidney.

Table IV. Dog: *Repair* of *aseptic wound*, 3 days.

Table V. Dog: *Repair* of *infected wound*, 3 days.

Compare carefully gross appearance of Ia and Ib.

Compare carefully gross appearance of IV and V.

EXERCISE IV.

THROMBOSIS, EMBOLISM, INFARCTION.

Table I. Rabbit: *Multiple bland infarctions* due to embolism produced by injection of foreign particles (tobacco seed). (Compare with multiple embolic abscesses due to injection of *Staphylococcus pyogenes aureus*, as seen in last weeks' exercise.)

Table II. Dog: *Air embolism* with graphic registration of changes in blood pressure, heart action and respiration. Ether anesthesia. Autopsy showing method of demonstrating air in heart cavities.

Table III. (a) Dog: *Thrombus* in jugular vein resulting from injury to intima caused by mechanical pressure.

(b) *Thrombus* formation in ligated artery (femoral).

Table IV. Sections of liver and spleen showing *hyalin thrombi* composed of agglutinated red blood corpuscles. From dog which received hemolytic (also hemagglutinative) serum (see Exercise I) and died after one hour; also sections from animals similarly treated, showing necrosis of the liver after twenty-four hours.

EXERCISE V.

HEART.

(All experiments under ether anesthesia.)

Table I. *Hydropericardium:* Experimental condition produced by introducing a large amount of salt solution into the pericardial cavity. Graphic registration of effect on heart action and arterial and venous pressure. Artificial respiration.

Table II. *Myocarditis:* Production of myocardial insufficiency by injection of alcohol into heart substance. Graphic registration of effect on heart action and blood pressure.

Table III. *Valvular Insufficiency:* Mechanical rupture of aortic valve by instrumentation through carotid artery. Graphic registration of effect on heart action and blood pressure.

EXERCISE VI.

LUNGS.

(All experiments under ether anesthesia.)

Table I. Graphic registration showing effect of double *Hydrothorax* on respiration, heart action and blood pressure. Hydrothorax produced by injection of salt solution.

Table II. Demonstration of the anatomical relations in the thorax under above conditions, *Atelectasis*.

Table III. *Emphysema:* The lungs of a guinea pig in the experimental condition known as anaphylaxis. The gross appearance of the lungs is similar to that of emphysema.

Table IV. (a) "*Deglutition*" *pneumonia;* due to foreign particles in bronchi.

(b) *Purulent pleuritis* (empyema) due to *Staphylococcus pyogenes aureus*.

Table V. *Edema of lung;* produced by infiltration of lung with salt solution. Graphic registration of effect on heart, blood pressure, and respiration.

EXERCISE VII.

Stomach and Intestine.

Table I. Experimental *Toxic gastritis*, due to (a) carbolic acid and (b) corrosive sublimate.
Table II. Experimental *Toxic gastritis*, due to (a) sulphuric acid and (b) nitric acid.
Table III. Experimental *Toxic gastritis*, due to caustic alkali (sodium hydrate).
Table IV. Experimental *Peptic ulcer*, produced by injecting serum beneath mucosa and by excising small portion of mucosa.
Table V. *Intussusception* and *Volvulus* of Intestine and *internal hernia.*

(All lesions produced under ether anesthesia followed by death from chloroform.)

EXERCISE VIII.

Pancreas.

Table I. Hog: Acute *hemorrhagic* and gangrenous pancreatitis and *Fat necrosis* following injection of bile into pancreatic duct. Lesions of twenty-four hours and forty-eight hours respectively.
Table II. Ligation of duct for period of two months; slight *atrophy;* no glycosuria.
Table III. *Experimental Diabetes* following extirpation of pancreas.
Table IV. *Phloridzin Diabetes.*
Table V. Tests for sugar in the urine of all of above.

EXERCISE IX.

Liver.

Table I. Multiple focal necroses of liver due to the injection of hemolytic and hemagglutinative immune serum.
Table II. Necrosis of liver due to prolonged inhalation of chloroform.
Table III. Obstructive Jaundice.
Table IV. Demonstration of a "spontaneous" cirrhosis of the liver in the dog.
Table V. (a) Sections illustrating microscopic picture in above lesions.
(b) Tests illustrating changes in the urine in I, II, and III.

EXERCISE X.

Kidney.

Table I. Acute nephritis in rabbit due to injection of 0.06 gm. potassium chromate. Essentially a tubular injury. 48 hours.
Table II. Acute nephritis in rabbit due to injection of 0.05 mg. rattlesnake venom. Essentially a vascular nephritis. 48 hours.
Table III. Acute nephritis with *edema* in rabbit. Due to injection of uranium nitrate and the administration of an excess of water by stomach tube. 5 days.
Table IV. Demonstration of factors influencing vascular reactions and diuresis in experimental nephritis. Oncometric studies.
Table V. (a) Urine of each of above showing albumin and casts.
(b) Stained sections of similar lesions.
Table VI. Hydronephrosis. 6 weeks after ligation of one ureter.

EXERCISE XI.

Hypersusceptibility (Allergy).

Table I. *Peculiar natural hypersusceptibility* to rabbit effluvia and to rabbit serum in case of a human patient.
Table II. *Experimental anaphylaxis:*

(a) Morbid anatomy and histology of the lungs of anaphylactic guinea pig.
(b) Physiology of anaphylactic "shock" in dog.

Immunity.

Table III. *Combination of toxin and anti-toxin:*
(a) Guinea pig injected with diphteria toxin; (b) guinea pig injected with diptheria toxin and protected by anti-toxin; (c) control animal injected with anti-toxin alone.
(d) Similar series with tetanus toxin and anti-toxin.
Table IV. (a) *Agglutination* of bacteria and of blood cells by specific immune sera.
(b) *Precipitation* of dissolved proteins by specific immune sera.
Table V. *Cytolysis:* (a) Hemolysis by means of specific immune sera in high dilutions, by natural hemolysins and by hematoxic agents, e. g., rattlesnake venom.
(b) *Fragility* of erythrocytes as shown by the use of salt solutions of varying tonicity.
Table VI. *Complement Fixation:* (a) Phenomenon with precipitins and other immune sera.
(b) Wasserman reaction.

EXERCISE XII.

Ductless Glands. Internal Secretion.

Table I. Local Vaso-constrictor effect of adrenalin as seen in rabbit's ear.
Table II. Effect of adrenalin on blood pressure as seen in dog.
Table III. Adrenalin glycosuria. Rabbit.
Table IV. Result of extirpation of adrenals. Dog.
Table V. Effect of extracts of hypophysis on blood pressure and diuresis, as seen in dog.
Table VI. Tetany in parathyroidectomized dog.
Table VII. Effect on tetany of injection of a calcium salt.
Table VIII. Review Exercise VIII, Demonstration III, Result of extirpation of pancreas.

Experimental Pathology and Physical Diagnosis.

EXERCISE XIII.

(In collaboration with Dr. W. T. Longcope.)

(All dogs under ether anesthesia and with tracheal canula, artificial respiration and mechanical ether dropper.)
Table I. *Normal dog:* By percussion and auscultation, note normal physical signs of respiration and the outlines of the lungs.
Table II. *Pneumothorax:* Normal dog. Note changes in physical signs produced by injection of air (200 cc.) into pleural cavity.
Table III. *Hydrothorax:* Due to injection of 400 cc. normal salt solution into pleural cavity. Note change in level of dullness on altering position of dog and of percussion notes and respiratory sound above and below level of fluid.
Table IV. *Acute Pleuritis:* Right side, 3 cc. turpentine injected into pleural cavity one hour before demonstration. Left side, same amount injected at beginning of demonstration. Compare friction rubs on both sides.

Table V. *Edema:* Bronchitis due to introduction of irritating substance as turpentine or ammonia into trachea. Study râles.

At autopsies on the above animals note:

Table I. Collapse of lungs and their position in relation to thoracic wall. Appearance of pleural surface.

Table II. Clamp tracheas before opening thorax, note condition of lungs.

Table III. Clamp tracheas, note level of fluid and compare with level determined by percussion. Note compression of lungs.

Table IV. Note amount and character of exudate on each side and appearance of pleura.

Table V. Note condition of bronchi; look for sclerosis and congestion.

(In connection with above, review Exercise VI.)

EXERCISE XIV.

(In collaboration with Dr. W. T. Longcope.)

(All dogs under ether anesthesia with tracheal canula, artificial respiration and mechanical ether dropper.)

Table I. *Normal dog:* Note normal heart sounds, over different regions of thorax. By palpation and percussion note area of cardiac dullness.

Table II. *Normal dog:* Thorax and pericardium opened. Note action of heart. Study heart sounds by auscultation directly over various regions of heart.

Table III. *Aortic regurgitation:* (a) Aortic cusp destroyed by instrumentation through left carotid artery. Note changes in heart sounds and cardiac dullness. (b) Same with thorax and pericardium opened; direct auscultation.

Table IV. *Aortic stenosis:* Thorax and pericardium opened. Aortic stenosis produced by tightening ligature about base of aorta. Note heart sounds and changes in shape, size and position of the various chambers of the heart.

(In connection with above, review Exercise V.)

These demonstrations, it is seen, include the presentation of necrosis and the degenerations, inflammation and repair, blood destruction and jaundice, thrombosis, embolism and infarction, certain lesions of the heart, lung, stomach, intestines, liver, pancreas, and kidney, and the problems of infection and immunity, of shock and hemorrhage and the physiology of the ductless glands.

With the exception of Exercises II, III, IV, XI, the experimental work was presented in connection with the general pathology and pathological histology of the subject under consideration. Physiological methods of graphic registration were used whenever possible; changes in the urine and other secretions demonstrated; and the methods of chemical diagnosis emphasized.

The planning of the course is no small matter and the labor of preparation * is great, but the actual demonstrations are not difficult; even if they were, the change in the attitude of the student toward pathology, which such a course brings about, makes it well worth while. This is particularly true of Exercises XIII and XIV which, given in collaboration with Dr. W. T. Longcope as a part of the course in Physical Diagnosis, were received with the greatest interest. To let the student produce, or see produced, certain anatomical lesions, and to allow him to study the alterations of function which result, applying thereto many of the clinical methods, and eventually at autopsy to correlate the disturbances in physiology with the anatomical changes, is, I believe, a most valuable preparation for clinical study in that it bridges the gap between pathological anatomy and clinical observation. Herein lies the chief value of courses in experimental pathology and pathological physiology.

* The success of this course, as given during the past year, is due in largest measure to the efforts of my assistants, Drs. A. B. Eisenbrey, H. T. Karsner, B. S. Veeder, and J. H. Austin, upon whose shoulders fell the burden of preparation.

A PROTEST AGAINST THE INDISCRIMINATE USE OF THE ORGANIC COMPOUNDS OF SILVER IN OPHTHALMIC PRACTICE.*

By SAMUEL THEOBALD, M. D.,

Clinical Professor of Ophthalmology and Otology, The Johns Hopkins University.

Whatever be the explanation, whether due to their chemical composition, the greater freedom with which they are used, or to their supposedly greater penetrating power, there can be no doubt that the organic compounds of silver—at all events, those with which I am familiar, protargol and argyrol—are responsible for many more cases of conjunctival argyria than ever was, or is, silver nitrate.

Before these compounds came into use, argyria of the conjunctiva was a rare condition—practically never seen except in old cases of trachoma. Now, it is relatively common, and is met with not only in chronic conditions, such as trachoma, but in acute affections as well, in which the silver treatment has been of comparatively brief duration.

I believe I am warranted in saying that I have never produced a case of ocular argyria from the use of silver nitrate. I regret that I cannot say the same as to the newer silver compounds. In several of my cases of gonorrhœal conjunctivitis in the adult decided staining, especially of the bulbar conjunctiva, has resulted from the employment of protargol, and the same has happened in a case of acute trachoma after only a few weeks treatment.

I have also observed a number of cases of similar character which have occurred in the practice of my confrères. A well-known physician of Baltimore was given a five per cent solution of argyrol for a mild chronic conjunctivitis. As its action was beneficial, his wife—in need only of glasses for the correction of a decided fault of refraction—also began to use it, and the two continued to employ it, p. r. n., until the physician had acquired one of the most marked cases of

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argyria I have ever seen, and his wife's eyes had become conspicuously stained.

Let me make it plain, that I have no unreasoning prejudice against these newer silver preparations. On the contrary, I have such faith in protargol, especially, that for some years I have employed it in the treatment of gonorrhœal conjunctivitis, both in the infant and the adult, to the exclusion of silver nitrate, and in trachomatous conjunctivitis, especially in the acute stage, it has also been my chief reliance.

It is, therefore, not against the *use*, but against the *indiscriminate*—or, perhaps, I might say indiscriminating—use of the organic silver compounds that I would protest. When a remedy is at hand, that is, at least, as efficacious as they are in the condition to be dealt with, that is cleanly and that cannot by any possibility produce the untoward consequences to which, as has been pointed out, they not rarely give rise, common sense would seem to dictate that it be given the preference.

These observations apply with especial force to the now almost, it would seem, universal habit, particularly among the younger generation of ophthalmologists and of general practitioners, as well, of employing argyrol or protargol, in the treatment of acute and chronic catarrhal conjunctivitis. This practice, in my judgment, and it is based upon abundant observation, is wholly indefensible, since we have a remedy—in a collyrium containing half a grain of zinc sulphate and ten or twelve grains of boracic acid to the ounce—that is cleanly, and that is not simply *as* efficacious, but is more surely and more promptly efficacious in these conditions than either of the silver compounds mentioned.

NOTES ON JAUNDICE IN PNEUMONIA.

By Fletcher McPhedran, M. B.,
Assistant Resident Physician, The Johns Hopkins Hospital.

Since Bettelheim and Leichtenstern first reported the occurrence of jaundice in lobar pneumonia, many explanations of its pathology have appeared in the literature. Bonilland considered it due to a transfer of the infection to the liver; Niemeyer to pressure of the hepatized lung on the torpid liver; Virchow and Leyden to an associated duodenal catarrh resulting in simple jaundice.

Banti[1] thought it due to a specific hæmolytic action of the diplococcus pneumoniæ, probably general in its distribution but maximal in the spleen. He found that hæmoglobinuria occurred in rabbits after infection with the pneumococcus. This hæmoglobinuria was not an index of the virulence of the germ, but was caused by a pneumococcus that had produced jaundice in man. In dógs he produced bilirubinuria, and concluded that in man the pneumoceoccus produced bilirubin which was ehanged in the tissues to urobilin, causing jaundice, and was excreted as urobilin.

Obermayer and Popper[2] investigated 134 cases of pneumonia, demonstrating pathological amounts of pigments (bilirubin, urobilin and biliverdin) in all urines, and found that these pigments had been described as urobilin, because the tests employed had not been sufficiently accurate to differentiate them. When the pigments were present in sufficient quantities to give the less delicate tests, jaundice appeared. They considered the jaundice hæmolytic and dependent upon the intensity of the infection. At autopsy they found large quantities of pigments in the hepatized and slight amounts in the congested areas, but felt that the color might be due to the pigments in the serum of the affected regions.

Herzfeld and Steiger[3] found pigments with great difficulty or not at all in the urines of patients whose sputa readily yielded them. As the pigments were only found when blood was mingled in the sputum, they concluded that they came from the extravasated red blood cells of the hepatization, and *in vitro* were able to show that the pneumococcus produced from hæmoglobin a body giving the color reactions of bilirubin.

Troisier[4] had meanwhile described the icterus as due to this local destruction, comparable to that observed in hæmorrhagic pleurisy, where diminished corpuscular resistance to hypotonie sodium chloride solutions is found, and where the bile pigments are produced apart from the liver. From this local area of destruction the pigments are carried throughout the body.

Lemierre and Abrami[5] found in two cases pure culture of the pneumococcus in the bile associated with no obstruction, but a definite degeneration of the liver cells. They thought all pigment must come from the liver.

It seemed that it might be a matter of interest to estimate the corpuscular resistance in a series of cases of lobar pneumonia with and without jaundice, in order to determine the question as to whether any of these cases might show a diminution of corpuscular resistance. During the last winter fourteen cases have beeen examined. The corpuscles were tested against solutions of chemically pure sodium chloride, progressively diminishing in strength from 0.6 per cent down to 0.26 per cent. The blood was received into a citrate solution in 0.85 per cent sodium chloride, washed three times with sodium chloride solution, and then the sedimented corpuscles dropped into tubes, each of which contained 3 cc. of the hypotonic sodium chloride solution. After two hours at 37 degrees C., the tubes were placed on ice and examined again after twenty-four hours. All glass ware was kept clean and the solutions sterile. Three readings were made, at the point of initial, marked and complete hæmolysis. Normally, initial hæmolysis should be at 0.42 per cent, marked at 0.34 per cent and complete at 0.26 per cent.

The urine was tested for urobilin, but in no case was there

any pathological increase. If the red blood cell counts were constant, one would expect a large number of new cells, which could be discovered by vital staining as described by Vaughan.[6] There was not any increase of the number of red blood cells so stained.

PNEUMONIAS WITHOUT JAUNDICE.

Name.	Race.	Sex.	R. B. C.	Initial.	Marked.	Complete.
1–G.	C.	F.	5,200,000	40	36	30
2–C.	W.	M.	5,232,000	42	36	32
3–C.	W.	M.	5,416,000	44	36	28
4–T.	W.	M.	3,300,000	42	36	32
5–G.	W.	M.	5,300,000	50	40	38
6–B.	W.	M.	4,900,000	44	36	30

PNEUMONIAS WITH JAUNDICE.

Name.	Race.	Sex.	R. B. C.	Initial.	Marked.	Complete.
7–J.	C.	F.	4,500,000	30	28	26
8–T.	C.	M.	4,704,000	38	34	26
9–S.	C.	M.	4,300,000	40	34	26
10–H.	W.	F.	5,250,000	40	34	28
11–J.	W.	F.	4,080,000	42	34	30
12–H.	C.	M.	5,280,000	44	38	30
13–F.	C.	M.	5,300,000	36	30	26
14–M.	W.	M.	4,800,000	38	32	26

Case No. 5 is noteworthy in view of the increased fragility of the cells found, but attempts to follow up the patient outside the hospital have been unsuccessful. He was not in the least jaundiced and showed no increase in reticulated cells.

It is interesting that in cases Nos. 7, 8 and 13, where clinically the jaundice was most intense, and bile pigments were readily found in the urine, the fragility was diminished, that is, the same condition obtained as was described by Chalier in obstructive jaundice.

The use of saponin (Merck's "purissimum") for hæmolysis as advocated by McNéill[7] was also tried, but the results in a series of control cases were not sufficiently accurate to warrant its continuance. He took a suspension of washed corpuscles in such an amount that there were about 50,000,000 cells, to which varying amounts of a saponin solution of 0.004 gm. to 100 cc. of 0.85 per cent sodium chloride were added. Then the mixture was brought to a volume of 2 cc. by more of the same sodium chloride solution and the number of red blood cells were counted on a Thoma Zeiss hæmocytometer. After incubation at 37 degrees C. for two hours, the remaining cells were enumerated and the amount of hæmolysis observed.

NORMAL ADULT.

Tube No.	R. B. C. suspension in NaCl 0.85 per cent.	Saponin.	NaCl 0.85 per cent.	Corrected Number R. B. C.	R. B. C. after 2 hours.	Per cent. of Hæmolysis.
	cc.	cc.	cc.			
1	.15	.08	1.77	43,000,000	41,700,000	46
1a	.15	.08	1.77	50,500,000	34,500,000	32
2	.15	.12	1.73	42,000,000	28,000,000	33
2a	.15	.12	1.73	41,200,000	27,600,000	34
3	.15	.16	1.69	42,000,000	28,000,000	33
3a	.15	.16	1.69	41,200,000	36,400,000	08
4	.15	.2	1.65	42,000,000	31,000,000	26
4a	.15	.2	1.65	40,300,000	26,200,000	35
5	.15	.24	1.61	42,000,000	1,000,000	97
5a	.15	.24	1.61	42,000,000	24,600,000	41

PNEUMONIA WITH JAUNDICE.

Tube No.	R. B. C. Suspension in NaCl 0.85 per cent.	Saponin.	NaCl 0.85 per cent.	Corrected Number R. B. C.	R. B. C. after 2 hours.	Per cent of Hæmolysis.
	cc.	cc.	cc.			
1	.13	.1	1.77	46,700,000	36,000,000	21
2	.13	.2	1.67	55,600,000	25,000,000	54
3	.13	.3	1.57	54,000,000	29,000,000	46

Now we see in the above that the same experiment repeated with the same technique on one individual gives widely variant results; for example, compare tubes 3 and 3a and tubes 5 and 5a. Nevertheless, there is a very slight, if any, difference in the figures of hæmolysis in the case of jaundice in pneumonia and in the normal adult.

Two cases, Nos. 7 and 8, came to autopsy; in neither was there any obstruction to the bile ducts, nor any destruction of liver cells, nor any increase in pigment found by the usual methods.

The number of red blood cells on admission was interesting; it averaged 4,840,000 for the males with jaundice and 4,400,000 for the females. In cases without jaundice, the number was 4,800,000 in males, and 5,200,000 in the only female. A series of typhoid fever patients comparable in age and duration of disease to this pneumonia series averaged 5,900,000 for males and 4,500,000 for females.

From the fact that the cells are in the lungs in such numbers, and that the pneumococcus has definite hæmolytic powers, together with the property of producing bile pigments, it is probable that the jaundice arises from the pigments produced in the lungs; but as all patients with pneumonia have this extravasation, there must be some other cause, perhaps a variation in the pneumococcus. This is not associated with the general increase in the fragility of the red blood cells.

SUMMARY.

1. In the fourteen cases there was increased fragility in only one case, this without jaundice: but in the cases with most marked jaundice there was, on the contrary, an increase in the corpuscular resistance.

2. The urine in no cases showed any excess of urobilin.

3. Bilirubin was present in the urine in three of the eight cases with jaundice.

4. Autopsy showed no evidence of special changes in the liver.

5. The blood counts showed such a loss that one must consider it as due to a sudden great destruction. This loss is probably due to the hepatization.

In concluding, I desire to thank Dr. W. S. Thayer for constant advice and assistance.

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ABDOMINAL LIPECTOMY.

REPORT OF TWO CASES.

By W. F. Shallenberger, M. D., Atlanta, Ga.,
Late Resident Surgeon, Maryland Hospital for Women, Baltimore.

This operation,[1] while no longer rare, is uncommon enough to warrant the report of these two cases, which came under my care at the Woman's Hospital in Baltimore.

Mrs. S., age 39, was sent to the hospital by her physician in March, 1910, for symptoms of a chronic appendicitis from which she had suffered for several years and which had been becoming more aggravated. She had a more or less constant pain in the right lower quadrant of the abdomen, which was quite severe at times. There was also nausea and vomiting occasionally, and constipation. No history of jaundice or urinary disturbance was obtained. The menstrual history was negative. The patient had had several children. Backache was the only symptom that suggested any pelvic trouble.

Fig. 1.

Fig. 2.

Fig. 1.—Healed incision in first patient showing the support the umbilicus gives. (Patient is standing.)
Fig. 2.—First patient, showing the abdominal supporter worn after operation.

Eight years ago the patient had an attack of typhoid fever, after which she began to grow very stout. Prior to this attack she had been of average size.

Examination.—The patient was quite fat, weight 227 pounds, of medium height. The outlines of her figure were good, except of the abdomen, which was very full and flabby, with a regular apron of fat that hung down over the symphysis when the patient was standing. One could pick the fat up in a great ridge or fold across the lower abdomen. The greatest deposit of fat was below the umbilicus, and it prevented the wearing of an abdominal supporter because of the flabbiness. The abdominal walls were firm beneath the fat.

On the right side there was tenderness over the appendix region, with slight muscle rigidity. The temperature was normal. The pelvic organs were normal except for a slight laceration of the cervix uteri and a moderate relaxation of the perineum. The backache I thought was due to the pendulous abdomen.

The patient received the suggestion that some of the fat be removed with much enthusiasm and was very eager that the operation be performed.

Operation.—A double incision was made from flank to flank below the umbilicus and embracing an elliptoid area of skin 45 cm. or 18 inches long, and 15 cm. or 6 inches at the widest part. The incisions were carried down to the fascia and the wedge or slice of skin and fat removed. Its weight was a trifle over 7 pounds.

Fig. 3.—The slab of skin and fat removed in the second case.

All the bleeding points were carefully secured and the fat of the two sides of the open area was brought together with a number of double figure-of-eight catgut sutures. The skin edges were then approximated. Three silver-wire sutures were first placed, and silkworm gut used to complete the approximation. Four rubber tissue drains were inserted, one in each angle of the incision and the others midway between the angles and the median line. These drains were removed on the third day.

Before the incision was closed, the peritoneal cavity was opened on the right side by a McBurney incision through the muscles and fascia and the appendix removed. It was large, injected and adherent.

The incision, which was 18 inches long, healed nicely and the patient had a rapid convalescence. She was greatly relieved, not only of the appendix symptoms but also of the backache. I have seen her a number of times since, and she is highly pleased with the results. We had an abdominal supporter made for her and this fits perfectly now. (Fig. 2.)

Mrs. P., a patient of Dr. Kelly, came to the hospital in

[1] Kelly, H. A.: Excision of the Fat of the Abdominal Wall—Lipectomy, Surg., Gyn., and Obst., 1910, X, 229.

December, 1910. She had a postoperative ventral hernia through an old midline incision. A hysterectomy had been done several years ago, and the patient had an incision infection and a peritonitis following. Aside from the hernia there were also extensive intestinal adhesions giving rise to considerable abdominal pain. There was a considerable deposit of fat in the abdominal wall.

Operation.—A double transverse incision was made from flank to flank, 38 cm. long and the two lines 12 cm. apart in the median abdominal line. The slab of fat was removed (Fig. 3) and the peritoneal cavity opened through the hernial sac. The intestinal adhesions were all separated and the hernia repaired by overlapping the fascia in the mid-line. The fat and skin edges were then brought together in much the same manner as in the first case, silkworm gut alone being used for the skin. Cigarette drains were placed in each angle of the incision.

The patient made an uneventful recovery and left the hospital greatly benefited by the operation.

In neither of these cases was there an umbilical hernia, and I wish to bring out a point here; namely, that where there is not an umbilical hernia the incisions should be made below the umbilicus, leaving it as a supporting point. This is shown in Fig. 1, where the highest point of the incision, as the patient stands, is seen to be in the median line below the umbilicus, and there is a tendency for the incision to sag down on each side.

Dr. Kelly did the first operation of this kind in 1899.[2] Since then he has had eight more cases, including the one reported here.

Maylord[3] reports three cases in which he did extensive lipectomy in fat women with umbilical herniæ. The first of his cases was done in 1903, and ten pounds were removed.

Weinold[4] reports a case in a woman with an enormously fat abdomen.

The results of such an operation are, to quote Dr. Kelly: "The removal of a slab of fat and a decrease in weight. Great addition to personal comfort generally. Convenience and comfort in dressing. Better pose in standing and better poise in walking. Increased activity. Cleanliness greatly facilitated. Figure changed from unsightly and awkward to one much more natural. The sensitive patient occupying afterwards a more normal and natural relation to society."

[2] Kelly, H. A.: Excessive Growth of Fat, Johns Hopkins Hosp. Bull., 1899, X, 197.

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IN MEMORIAM.

DR. CHRISTIAN ARCHIBALD HERTER.

In response to an invitation issued by the President of the Johns Hopkins University and the committee on the Herter Memorial Lectureship a meeting in memory of the late Dr. Christian Archibald Herter was held in the lecture room of the Physiological Laboratory of the Johns Hopkins University on Thursday, October 5, 1911, at 3 p. m.

Drs. W. H. Welch, W. S. Halsted, and J. J. Abel of Baltimore and E. Dunham and Simon Flexner of New York, spoke of various aspects of the life and work of Dr. Herter and paid tribute to his character and his services to medical science.

The following minute was adopted and was subsequently read to the audience assembled at four o'clock to hear Professor Kossel's second Herter lecture, who expressed their respect and approval by a rising vote:

MINUTE

The medical faculty and other members of the Johns Hopkins University, as well as all assembled at the delivery of the sixth series of lectures upon the Herter Foundation, desire to place upon record their sense of the great loss sustained by American Medicine and by medical science in the death of Dr. Christian Archibald Herter on December 5, 1910.

The initiation of Dr. Herter's fruitful activity as a scientific investigator by his work as a graduate student in this University and his active interest in the development of this medical school are sources of especial gratification to the University. Upon this occasion especially we recall with grateful appreciation his generous benefaction in founding, in association with Mrs. Herter, a lectureship which has been and will continue to be a fountain of inspiration and instruction to our faculty and students and to the medical profession.

In the life and work and character of Dr. Herter we recognize the manifestation of rare gifts of intellect and of heart and high-minded devotion to the highest ideals of our profession and of scientific medicine. By valuable contributions to knowledge, by wisely directed and generous material aid in the promotion of medical and biological science, by judicious counsel and active effort and by the widely felt influence of a richly endowed and singularly attractive and cultivated personality, Dr. Herter rendered memorable service to American medicine in behalf of higher professional standards and wider recognition and cultivation of medical science.

In this University and elsewhere the memory of Christian Archibald Herter will be cherished not only as that of a generous benefactor, but also "as a presence to be felt and known" exemplifying love of beauty, broad humanity and loyalty and devotion to the best ideals of the physician and the student of man and of nature.

We desire to express our sympathy with Mrs. Herter and her children in their bereavement and that a copy of this minute be transmitted to them.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XXII is in progress. The subscription price is $2.00 per year in the United States, Canada, and Mexico; foreign subscriptions $2.50.

NOTES ON NEW BOOKS.

The Principles of Pathology. By J. George Adami, M. D., etc. Vol. I. General Pathology by J. George Adami; Vol. II. Systemic Pathology by J. George Adami and Albert G. Nicholls, M. D., etc. Second Edition. Revised and Enlarged. Illustrated. (*Philadelphia and New York: Lea & Febiger. 1910.*)

This is not a new book, but is already in its second edition, so that there can be no question as to its value in satisfying a general need. The scope of such a book should be determined to some extent by the requirements of those for whom it is intended, and if any criticism is to be offered upon a text-book such as this, which is designed for the use of students as well as physicians, it is that here an attempt is made to cover in some way the whole field of pathology, including the fields of those subjects which are preparatory in a sense to the study of pathology, and upon a knowledge of which pathology depends. This encyclopædic plan has resulted in the production of two great volumes each of about a thousand pages, which are really more than the students in our schools of medicine can read and master in their course in pathology. It is perfectly true that, were the courses in pathology commensurate with their importance to the future physician as the foundation of his thought and action, he might readily require even more. For the practising physician who wishes to refer to a text-book of pathology these two volumes are excellent; but it is for the leisurely pathologist who sits down to peruse the new book that it—at least the first volume—affords pleasure. The second volume is a collaboration and in it the attempt appears to be made to apply the general principles to all the tissues and organs —an attempt which often leaves the impression given by the perfunctory fulfillment of a task, and which leads to an endless repetition of ideas which comes sometimes to involve the illustrations.

The prime effort is expended, apparently, upon the discussion of general pathological principles which, as everyone must agree, are rightly limited to those which affect all the tissues, and such things as the disturbances of the circulation which are so commonly treated as general pathological processes, are relegated to the chapters on the pathology of the circulation. In this way the general pathology becomes the pathology of the cell at large, its nutrition, its growth, its various activities and reactions to outward influences, and its transmission of its own characters.

In order to discuss all these things intelligibly, Dr. Adami occupies 200 pages with the normal anatomy, physiology, and chemistry of the cell, which then leads him to the problems of heredity. All this is very clearly written and deals with the more modern views of the changes which go on within the cells under more or less normal conditions. The treatment of the various causes of disease is superior to that in most books, in that he spends less space upon the minute descriptions of every kind of bacterium and animal parasite—things which can be studied to far greater advantage in special books on these subjects. Two or three of these chapters are devoted to a general review of malformations—again a subject of such enormous proportions that any general pathologist is wise to treat it summarily. The next section which discusses inflammation with fever and immunity is admirable, as one might expect from Dr. Adami's previous monograph upon inflammation. In speaking of repair, hypertrophy, regeneration, etc., he refuses to accept Weigert's idea as to the reasons for new growth after injury. This dictum of Weigert that such new growth is essentially repair due to the disturbing effect of a break in equilibrium, and not the direct effect of stimulation even in a minimal injury, has been very powerful among pathologists for years, and yet Dr. Adami presents the opposite views so forcibly that one can scarcely help wavering and finally accepting them. Doubtless there is much truth on both sides and Dr. Adami would be the last to maintain a narrow point of view. In speaking of tumors he considers the routine material adding only his plan of dividing tumors into "lepidic" and "hylic" according as they are derived from lining cells or from solid tissues. This, it seems, is merely a restatement of the idea which Hansemann first put forth and which has been in the minds of many, that probably it would be simpler and easier to give up the attempt to trace tissues back to their origins, and to content oneself with their adult form as a basis for their morphological classification so that a covering layer of cells without intercellular substance is, for Hansemann, epithelium no matter what its primary source, and tumors springing from it are named accordingly.

It seems of temporary importance at any rate to strive over these histogenetic questions with reference to tumors for the discovery of the etiological factors underlying the changes in the vital characters of the cells involved will surely render vain a great part of that.

The discussions of regressive tissue changes are especially good and the volume ends wtih their ultimate outcome—death.

As to the book itself, it may be said that the printing is good enough, the illustrations are fair—it is by no means richly illustrated and with the exception of diagrams and a few colored plates, nearly all, at least in the second volume, are from photographs. Literature references are given at times but they are not very complete nor always accurate—on page 384 volume 2 and page 445 volume 1, the work of Opie has been flatteringly but quite unfairly ascribed to the present reviewer.

On the whole there is no doubt that this is the best book on pathology in the English language. It brings forward all the usual material and discusses all the morbid processes and anatomical changes and the problems connected with them with eminent fairness, clearness and sanity. It errs perhaps a little as far as the mere medical student is concerned on the side of profusion and in theoretical discussion. It is not so much the work of a man whose mind is filled with the fresh pictures in all their colors, of the lesions he has just seen at the autopsy table, or with the movements of levers connected with the heart of his experimental animal, as that of the philosophic person who remembers these things and formulates clearly the explanations which are by no means so clear to the fresh observer.

Merck's Manual of the Materia Medica. Fourth Edition. (*Merck & Co.: New York, 1911.*)

This small pocket-book will be found useful by many practitioners. It is divided into four parts: 1, The Materia Medica as in actual use to-day by American Physicians; 2, Therapeutic Indications and Prescription Formulas for the use of the Materia Medica, and Bedside Diagnosis; 3, Classification of Medicaments; and 4, Miscellany. It is neatly prepared and can be safely recommended.

What Shall I Eat? By Dr. F. X. Gouraud. Translated by Francis J. Rebman. Price, $1.50. (*New York: Rebman Company, 1911.*)

It is rather difficult to know what view to express about this work for it is evidently intended both for the medical and general reader although it can hardly be regarded as satisfactory for either of them, which is generally the case in such works. Of the importance of proper diet there is no question, but it is

doubtful if this work gives much aid in deciding what is proper. The various forms of food are taken up in detail and the general composition stated. After this comes a statement of the effects of each article of food in particular diseases. There is everywhere a tendency to quote such varying opinions that one is frequently left in doubt as to what is really advised. On the much debated question of vegetarianism there is rather a good section in which the writer takes the view that it is by no means advisable for general application; it may be a good regimen for many but does not suit all.

There are a number of very curious statements here and there. Thus the opinion is quoted "that meat is not an aliment fit for the mind." Again meat is forbidden in "colonial diseases," whatever these may be. The author refers to a case of his own in which a man contracted typhoid fever "from eating a partridge that was too far advanced." Of course he did not contract typhoid fever from any such cause. He may have suffered from one of the forms of meat poisoning which sometimes resemble typhiod fever. In many places it is a little difficult to know what the author means, as when he says that "the arthritics form a family that disregards all restrictions as to diet with the utmost audacity." Then we find the statement that bread is a source of "humoral acidity," which sounds ominous but it is not easy to understand what is meant by this. Coffee is referred to as a "nerve food"; it certainly is rather a curious use of terms in a work devoted to a discussion of diet. The author condemns the drinking of water before or after eating but gives no reason for this sweeping statement. The probability is that many people are greatly aided by taking water before meals. Neither does he give any reason for the statement that ice water, or even cold water, is "ever harmful."

In the discussion of alcohol the following comment is made: "Normally alcohol acts through the kidneys. It is burned up there and eliminated in the form of water and carbonic acid." This certainly seems rather a curious statement. Then again alcohol is described as being a nervine and is stated to cause a "turmoil of excessive excitation, which is fatally followed by pronounced depression. . . . ." This succession of alternatives is said to lay the foundation for gastritis and cirrhosis of the liver.

That the book is intended for popular reading is shown by the inclusion of a glossary. It would have been well if this had been more carefully edited. Thus we find that atheroma is defined as a tumor. This is perhaps interesting as a guide to the derivation of the term but of course is not accurate in reference to its usage in this work or in medical writing.

We can not see that a book such as this is of any value. It is not likely that it will be of any special help to the members of the profession and certainly for the public it can not be regarded as a satisfactory guide. Take such a statement as this, "the habit of finishing every meal with a bit of cheese often enough proves fatal to men of the world." This suggests many questions which no doubt occur to the reader. Such a statement makes one distrust the writer of it as a good guide in matters of diet. Altogether the reading of this work will give the medical reader much more amusement than profit, but even so it can not be advised as worth the time.

A Practical Medical Dictionary. By Thomas Lathrop Stedman, A. M., M. D. Illustrated. Price, $5. (*New York: William Wood & Co., 1911.*)

Dr. Stedman has had much experience in editing medical works, and this dictionary is at once an evidence of his learning and skill. It is, we believe, the best of its kind in the English language. Those interested in the origin of words will take especial satisfaction in using it, since, so far as possible, the editor has traced back each word to its source. Others will note with equal pleasure his effort to use correct derivatives. not hybrid words made from both Greek and Latin, but whenever possible a pure Greek or Latin word. Such efforts are however, as Dr. Stedman well recognizes, often vain. Take for example the word "appendicitis," which is a barbarism but it is so well established by use that there is no hope of changing it. Dr. Stedman shows that the proper term would be "scolecoiditis"; this sounds strange to our ears, but had it been as long in use as appendicitis, it would be no stranger to us than many surgical terms commonly used. Purity of language should be aimed at by all who wish to write correctly and this is all important in scientific language. Therefore this dictionary will be especially helpful to all medical authors.

What matter to admit in a dictionary and how it should be arranged (set up in type) are largely questions to be left to the editor's taste. Much is to be said in favor of the arrangement adopted by Dr. Stedman but as to the introduction of chemical terms and signs there may well be a difference of opinion. By admitting these Dr. Stedman has made his dictionary more complete than any other. His use of the Basle Anatomical Nomenclature is but another proof of the really scientific quality of the work. The proper selection of illustrations for any dictionary is always a puzzle but those found in this one may be said to be as satisfactory as in any.

The publishers as well as Dr. Stedman are to be congratulated in this new dictionary, which all medical writers will be glad to possess. The make-up of the volume is pleasing; the paper is good, the type excellent both in size and distinctness, so that with admirable spacing the use of the dictionary is made a pleasure.

Diseases of the Genito-Urinary Organs. By Edward L. Keyes, Jr., M. D., Ph. D. Price, $6.00. (*New York: D. Appleton & Co., 1910.*)

This work of Keyes is probably one of the best that has so far been published for the general use of the student. The subject is dealt with clearly and concisely, yet at the same time thoroughly. The illustrations, which are found in profusion, are for the most part very good. The text is well written and makes very interesting reading.

The author has adapted the theory of Ciechanowski concerning the etiology of prostatic hypertrophy. This very attractive theory, which holds that chronic prostatitis is the direct cause of hypertrophy has, however, very little to support it from a statistical or pathological standpoint.

The value of the book is materially enhanced by the chapters on syphilis.

The volume as a whole is replete with practical information, and will prove to be a useful and valuable guide, not only to the general practitioner and student, but also to the specialist.

Prevention of Infectious Diseases. By Alvah H. Doty, M. D., Health Officer of the Port of New York. (*New York and London: D. Appleton & Co., 1911.*)

This little book of less than 300 pages is a valuable addition to the literature dealing with infectious diseases, expressing as it does the point of view of a health officer with many years' experience in this field. Such diseases as smallpox, yellow fever, typhus fever, plague and cholera are presented in detail from the sanitary standpoint, and the proper preventive measures to be employed in these diseases emphasized. The older theories which seek to account for the spread of infectious diseases by fomites, are contrasted with the newer theories in which the rôle of insects and bacillus carriers occupy a position of primary importance. The author is somewhat dogmatic in his treatment

of the subject, frequently expressing his personal individual opinion without giving his readers the facts and observations upon which his opinions are based. There is but little citation of authority, and a frequent and unnecessary repetition of statements of general import. The subjects of disinfection and disinfectants are particularly well handled. Despite a rather obstruse style and a general, rather than a special discussion of the subject matter, the book may be recommended to medical students interested in preventive medicine.

Die Faeces des Säuglings und des Kindes. Die Bedeutung Und Teehnik Ihrer Untersuehung. Von Dr. Adolf F. Hecht. Price, Mk. 8. (*Berlin und Wien: Urban & Sehwarzenberg, 1910.*)

This monograph on the feces of infants and children treats in an exhaustive manner the composition of the feces in the norm and under pathological conditions, noting the significance of the result obtained thus far. The methods of the examination of the feces are given in such a manner as to render the book very valuable for workers in this field. The book is not only of value to the pediatrician but will be welcomed by the student of nutrition.

S. A.

A Text-book of Bacteriology: A Praetical Treatise for Students and Practitioners of Medieine. By Philip Hanson Hiss, Jr., M. D., Professor of Bacteriology, College of Physicians and Surgeons, Columbia University, New York City, and Hans Zinsser, M. D., Professor of Bacteriology, Leland Stanford, Jr., University, Palo Alto, California. (*New York and London: D. Appleton & Co., 1910.*)

The appearance of a new text-book in any subject relating to the medical sciences is not usually a matter for congratulation, but the publication of a new treatise on bacteriology in 1910 by Dr. P. H. Hiss, Jr., Professor of Bacteriology in the Columbia University, New York, and Dr. Hans Zinsser, now Professor of Bacteriology in Leland Stanford, Jr., University, may be regarded in an entirely different light. In addition to a number of fairly mediocre text-books in this field which the American medical students have had to rely upon for some years, two publications of surpassing value have appeared within a comparatively short time, one the careful painstaking American edition of Muir and Ritchie by Harris, and the other the General Text-book of Bacteriology by E. O. Jordan, of the University of Chicago. Both of these books have been highly recommended to the readers of the Bulletin. Hiss and Zinsser's work is thus the third of the really first-class books on this subject in English. It is far more comprehensive in its scope than either of those previously mentioned, and the reputation of its authors for scientific investigation of the highest character is at once a guarantee of the excellence of the work. We have now been able to utilize this text-book in teaching two classes in bacteriology and our experience in its use has only fulfilled the highest expectations formed originally. Throughout the whole volume a strong conservative tone is manifest. Facts are not accepted without due evidence, doubt is always expressed when the opportunity for doubt exists, and allowance is always made for the various interpretations which can be drawn from reported observations.

The book consists of over 700 pages divided into 54 chapters. These chapters are grouped under five different sections. Section I deals with the General Biology of Bacteria and the Technique of Bacteriological Study, Section II with Infection and Immunity, Section III with Pathogenic Microorganisms, Section IV with Diseases of Unknown Etiology, and Section V with Bacteria in Air, Soil, Water and Milk. In the first section the historical side of the subject is well presented but possibly too concisely for a work so pretentious as this and in our opinion the great and fundamental value of Koch's early work on bacteria is not properly indicated. It was Koch's work on anthrax in 1876 that began a new era in bacteriology, and his discovery of the tubercle bacillus and the cholera vibrio that directed the attention of the medical public to this field. The chapters devoted to the biological activities of bacteria are clearly written, and in those dealing with microscopic study and staining methods, and with the preparation of cultural media, there is a wealth of detail gratifying alike to instructor and student.

In Section II on Infection and Immunity nearly one hundred and fifty pages are devoted to the subject and nearly every phase of it is considered. Toxins, antitoxins, lysins, agglutinins, precipitins, opsonins, aggressins, and anaphylaxis are all considered in detail. The theories of immunity are presented with great clarity and are not too much amplified. Especial emphasis is laid upon the technique of serum reactions, material rarely presented in text-books and upon the practical bearing of the facts and problems of immunity upon the science of medicine.

Section III is devoted to the Pathogenic Microorganisms which affect man. They are described with great accuracy and the lesions with which they are associated in man and which they produce in animals are carefully portrayed. Especially to be praised is the description of the cultural reactions of such organisms as the pneumococcus and streptococcus, the typhoid bacillus and the dysentery bacillus. In this section the authors have made no particular attempt to apply correct botanical names. This may be regarded as an unwise procedure from a scientific standpoint, but possibly justified in a text-book written primarily for students of medicine. The chapter on the leprosy bacillus was evidently prepared before the work on this organism by Clegg in the Philippine Islands and Duval in New Orleans, although the book apparently went to press after the important investigations of these authors had come to light. This is extremely unfortunate since it renders a thorough revision of this chapter necessary and fails in its present form to give any credit to investigators who have succeeded in cultivating organisms which have defied the attempts of some of the foremost men in the field of bacteriology. Another achievement of American workers, the solution of the etiology of hog cholera, is not presented, but this may be excused on the plea that this text-book is devoted to the organisms which infect man. The value of this work, however, and the relation of the fact brought out by Dorset, McBride and Bolton, that hog cholera is due to a filterable virus, to problems of infection in man and to the general subject of immunity, might have been made an excuse for reporting in detail what we must regard as one of the greatest contributions of American bacteriologists.

In Section IV, devoted to Diseases of Unknown Etiology and Section V, on Bacteria in Air, Soil, Water and Milk, the main points of importance in this connection are presented clearly and concisely.

The book is highly to be commended both to the medical student and the practicing physician. From the standpoint of the instructor it satisfies a need long felt in teaching the subject of bacteriology, and will, we believe, become one of our most popular text-books on this subject.

W. W. Ford.

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THE LIFE AND WORK OF ROBERT KOCH.

By William W. Ford, M. D., D. P. H.,

Associate Professor of Hygiene and Bacteriology, The Johns Hopkins University.

Paul Ehrlich, possibly the greatest mind in modern medical Germany, certainly the most prolific investigator in those fields of Medical Science in which his path has lain, said when Koch died that our entire knowledge of the infectious diseases and the various related branches of learning rests upon the foundations which he established; that he devised the methods which gave science the posibility of solving the problems in immunity on an exact experimental basis, the problems of immunity which Pasteur for the first time freed from the confusion of pure empiricism: and that even in the realm of experimental therapy Koch holds the first place, since he taught the world how to transmit the infectious diseases artificially from animal to animal, thus enabling us to apply therapeutic measures experimentally.

This praise by Ehrlich seems at first an extravagant tribute of admiration for a devoted friend and an honored colleague; but when we remember that every well-trained physician and surgeon of the present generation uses in his daily work the knowledge which came from the investigations of Koch; that every properly organized medical school and hospital has a laboratory founded on the methods which Koch devised and the apparatus which he invented; that every municipality in the fight against the great pestilences of the world, cholera, tuberculosis, typhoid fever, diphtheria, and in the efforts to provide for its citizens milk, water, and food which cannot serve as the vehicle of infection, depends for its preventive measures upon the doctrines which Koch proved; when we reflect that all modern bacteriology has been made possible by the discoveries of Robert Koch, then we are minded to regard Ehrlich's tribute as expressing even less than the truth.

Let us inquire into the circumstances of Koch's life and study for a moment his early publications to try and determine why he occupies such a pre-eminent place in medical science. Robert Koch was born in Klausthal in the province of Hanover on December 11, 1843. According to Gaffky, who has given us the most intimate account of his teacher and predecessor at the *Institut für Infecktions-Krankheiten,* Koch's family had lived in Klausthal for a number of generations, and had been for some years in the employ of the government. His father was a man of considerable scientific attainment, whose reputation spread beyond the little district in which his activities were centered, and who was honored by the Prussian government with the title of *Bergrath,* or as we may say expert mining engineer. Koch himself was one of thirteen children, two daughters and eleven sons. Two brothers dying in infancy left him among the eldest of the sons. His mother was a hard-working woman, whose domestic cares and responsibilities prevented her from devoting much attention to the rearing of her numerous progeny, and his father from the nature of his work was compelled to absent himself from the home for much of his time. Koch was thus left to grow up in a crowd of wild and untrained boys. He attended the Klausthal Gymnasium, in which, contemporary accounts tell us, the instruction was poor and discipline lax. He took an active part in the school life, was an excellent athlete, was a member of a school society known as Concordia, and sang, but without great success, in

a choral union, or as we would express it, was a member of the Glee Club. During his school life his chief outside occupation was with his father, whom he accompanied on long rides and walks over the hills and valleys of the surrounding Harz country. He early showed a passion for natural science and made numerous collections of minerals, plants, and small animals. His reading along the lines of geology, zoölogy and botany was extensive and during his entire life and work he kept up this active interest in the branches of learning collateral to the science of medicine. Koch thus enjoyed in his early youth the free out-door life of a boy brought up in the country, developing a rugged physique and great powers of endurance.

He was intended by his father for a merchant, the rapidly growing commercial cities of northern Germany like Hamburg and Bremen with their world-wide commerce offering the sons of Government officials peculiar advantages for a practical career. About the year 1860, however, the worldly condition of the father was greatly improved—we do not know the exact source of this enhancement of income—and he was enabled to offer the son a University training. We thus find Koch in 1862 leaving the Klausthal Gymnasium, wending his way to Göttingen and entering upon the study of medicine. His idea at that time seems to have been to train himself to be a ship-surgeon.

At the time Koch entered the University of Göttingen the faculty there included a number of men who left their marks on science. The senior among them was the chemist Friedrich Woehler, who in 1828 had accomplished the synthesis of urea. Others were the pathologist Wilhelm Krause and the physiologist George Meissner. By far the most important man in Göttingen, however, was the anatomist Jacob Henle, whose scientific work and mental grasp were so wide that his writings covered the field of physiology and pathology as well as anatomy. It is interesting and important to note that Koch came into intimate relationship with Henle, who evidently made a strong impression upon him.

In the year 1865, the medical faculty offered a prize for the best dissertation upon the structure of the uterine nerves. In the competition which resulted, two prizes were awarded, one to Robert Koch for a thesis which bore the title *Ueber das Vorkommen von Ganglienzellen an den Nerven des Uterus* and was inscribed with the Latin motto, *Nunquam otiosus;* a second prize going to a fellow-landsman of Koch's, Adolf Polle. Four weeks later, on July 18, 1865, Koch was appointed assistant in the Pathological Museum of which Krause was the director. This appointment offered him the opportunity of acquiring a thorough training in pathological and microscopical technique, a training which gave him afterwards the ability to guide his early footsteps groping in the dark maze of microorganisms by the true light of pathological anatomy. At the same time that Koch served as assistant in pathology he was engaged in original work in the Physiological Institute under the direction of Meissner. He made a study of the excretion of succinic acid in animals fed exclusively on meat and fat. Koch was unwilling to limit his observations to the lower animals but endeavored to work out the problem by making himself the subject of experimentation. He ate half a pound of butter daily and estimated his output of succinic acid. Unfortunately he undertook these experiments in the hot days of summer and after five administrations of this fat-rich diet, his stomach revolted, he developed a violent attack of gastric catarrh and was compelled to finish his work upon the less sensitive animals.

In January, 1866, Koch finished his academic career, passing the *examen rigorosum* with the mark *eximia cum laude* and three days later was given his doctor's degree on which occasion he delivered in Latin an address on the subject "Succinic Acid in the Human Body." Owing probably to his previous thesis on the ganglion cells of the uterus, he was not compelled to present a thesis on taking his degree. In March of the same year Koch passed the state examination in Hanover, having spent the intervening time in postgraduate study in Berlin. He then became an assistant in the General Hospital in Hamburg for a short term of three months and in October took a place as physician to the Asylum for Idiots in Langenhagen near the city of Hanover, where he remained until July, 1868. He practiced for a short time in the little town of Niemegk but in 1869 moved to Rakwitz in the Province of Posen. From Rakwitz he enlisted as a surgeon in the Franco-Prussian War and after his return in 1872 secured the position of *Kreis-physicus* or district physician in the town of Wollstein.

Here in Wollstein Koch remained for years busily engaged in a general country practice of medicine. He was forced to take long rides over rough country roads by day and by night, and minister to the needs of a people in the humblest circumstances. He was out of touch with University affairs which he loved. He was outside the circle of intellectual activity, the stimulus to great endeavor. And yet from the time of Koch's arrival in Wollstein, we know that he occupied himself unceasingly in attempts to solve the most important questions in medicine of his day and generation. We know that he fitted up for himself a laboratory, setting aside a portion of his consulting room for this purpose. We know that immediately after his arrival there he purchased a new microscope and a microtome and that in his improvised laboratory he installed a piece of apparatus, the use of which he had learned in the Physiological Institute at Göttingen, an incubator or thermostat which could be kept at the body temperature. We know that Koch devoted all his spare time to the study of a disease of animals widely spread in the district where he lived, anthrax or splenic fever, and that he carried out all sorts of experiments in his study of this disease. We do not know why Koch did not lapse into the respectable mediocrity which his position in life and his professional attainments made for him the line of least resistance. Something of his youth, when his chief pleasure was the amateur collection and dissection of plants and animals, something of the influences with which he was surrounded in the years at Göttingen, possibly the inspiration of his teacher and master Henle, something it was which kept Robert Koch from degenerating. Something kept his

fingers busy with slides and coverslips, his eyes glued to the microscope in all the spare hours which he could snatch from the exacting duties of a country practice. During the first four years of this period Koch seems to have said nothing of his work and only in the year 1876 when he was thirty-three years old, and ten years after his graduation from Göttingen did any inkling of his results reach the scientific world.

To understand the significance of Koch's first publication we must glance for a moment at the bacteriological work which preceded it. For 100 years after the discovery of the microscope by Athanasius Kircher and the improvement in lenses by Leeuwenhoek, which revealed to the astonished eye the countless structures belonging to a finer world, the attention of investigators was centered upon these minute bodies and speculation was rife as to the possible rôle they might play in nature. So confused were the ideas of scientists, nevertheless, and so puzzling were the findings of the microscope that the great botanist Linnæus grouped all the microscopic living forms under one division which he named "chaos." Gradually, however, more and more definite conclusions could be drawn from the many observations. Plenciz, for instance, in an accurate analysis of the symptoms of disease brought forward convincing arguments for the doctrine of "contagium vivum." Spallanzani and later Schultze pointed out that the development of living organisms was the cause of putrefaction and Müller and Ehrenberg by exact morphological studies demonstrated the existence of constant differences in the various bodies seen with the microscope. The year 1837 was especially fruitful in observations of permanent scientific value. In this year Donné described for the first time living microorganisms in pathological conditions. In pus from a syphilitic chancre he found minute forms which he termed vibrios, and with material containing these vibrios he inoculated the skin of the thigh in some of his patients. On the following day he noted the appearance of a typical pustule containing a sero-purulent fluid in which vibrios like the original were to be found. Despite the fact that Donné obtained these vibrios from cases of typical syphilis, and showed that they contained infectious material, he was not convinced that they were the cause of the disease. In Paris, in 1844, he announced that the vibrios previously seen were in all probability accidentally present on the surface of the chancre. In the year 1837 also Cagniard-Latour and Schwann each made independently the observation that the small round bodies first found by Leeuwenhoek in beer and wine could be seen to increase and multiply step by step as the fermentation of the beer and wine advanced. They suggested that these bodies were minute plants and the cause of the fermentation, Turpin later giving them the name *Torula cerevisiæ*. The idea that disease and fermentation were similar processes was by no means new to medicine and if the one were due to the growth of microorganisms, the other might also be due to this factor. In the year 1837, we thus have the first clear formulation of the germ theory of disease which rested upon any definite observations. This year also saw the discovery by Bassi that muscardine, the contagious disease of the silk-worm was caused by a minute plant, a discovery which gave instant confirmation to the theories of Latour and Schwann. Soon all sorts of microscopic forms were described in diseased conditions and their etiological relationship to these conditions accepted without question, but the resulting confusion was so great and the bar to further progress so strong that Jacob Henle, then a Privat-docent in the University of Berlin, was stimulated to challenge the claims of the many investigators who attributed disease to bacteria. In 1840 in his *Pathologische Untersuchungen*, in an essay entitled *Von den Miasmen und Contagien und von den miasmatisch-contagiösen Krankheiten*, he called attention to the various conditions which had to be established in order to show that bacteria were the cause of disease. "Before microscopic forms," said Henle, "can be regarded as the cause of contagion in man they must be found constantly in the contagious material, they must be isolated from it and their strength tested." The postulates of Henle seem so near the truth as we see it today, that we are apt to transfer them directly from the science of 1840 to the science of 1900, forgetting that the state of knowledge at the time Henle wrote could give him no adequate conception of the morphological and physiological properties of bacteria as at present understood.

Nevertheless the rigid proof demanded by Henle, made the most profound impression upon the thought of his day. The wild and reckless speculation ceased. Fortunately the work went on and the observations continued. During the next decade a host of parasites was described, many of them belonging, we now know, to the higher fungi, and to this period we owe such terms as oïdium, aspergillus, trichophyton, and leptothrix.

In the year 1857 Pasteur following the lead of Spallanzani and Schultze, by his demonstration of the special resistance to heat of certain bacterial structures which we now recognize as spores, dispelled from the world the fascinating doctrine of spontaneous generation. He next showed that as Latour and Schwann had taught for beer and wine, the fermentation which resulted in lactic, acetic, and butyric acid was also occasioned by microorganisms which differed from each other in morphological and biological characteristics and that the diseases of wine and beer were accompanied by other forms than those found under normal conditions. He thus established on a firm basis the doctrine of the existence of definite kinds of microorganisms having definite physiological properties. Pasteur, however, was interested largely in the study of microscopic organisms in bulk, and in determining the effects brought about by the development of these organisms under different conditions. He had little or no interest in morphological studies and the necessity of obtaining pure cultures and of studying the action of isolated species apparently was not clearly faced by him.

These observations upon fermentation were confirmed almost at once, but in an indirect way, by the apothecary Lemaire who for years had busied himself with the study of carbolic acid. Lemaire showed that the addition of minute traces of this acid

to fluids fermenting from the development of microorganisms stopped this action while the addition of the same material to solutions containing diastase or similar substances was without effect. The carbolic, according to Lemaire, inhibited the development of the living plants but could not stop the chemical changes superinduced by the presence of the true ferments. The importance of this observation did not escape Lemaire, who suggested that the suppuration of wounds might be prevented also by the addition of carbolic acid, if the suppuration were really due to living parasites. Shortly after, the brilliant young English surgeon, Joseph Lister, thoroughly imbued with Pasteur's ideas on fermentation and its relation to disease, began his wonderful experiments upon the healing of wounds. He seems to have been unfamiliar with Lemaire's observations, gaining his first idea as to the efficacy of carbolic acid in the destruction of microorganisms from the work which was done with this acid in the disposal of sewage near the little town of Carlisle. The observations of Lister, by means of which he developed his antiseptic technique, form one of the great chapters in surgery as well as in bacteriology and we all know how far-reaching the influence of this work has been. Lister was actuated in his experiments, however, mainly by the idea that the poisonous germs were in the air and that their access to the wounds must be prevented, a point of view which we now recognize to have been based upon insufficient knowledge as to the etiology of infections. At no time did he offer any evidence to show that a definite pathological condition was due to the development of a particular bacterial species.

The first observation of a characteristic microorganism in a definite disease is apparently that of Pollender, who, in 1849, found the bacillus of anthrax in the blood of an animal dead of splenic fever. The following year this was confirmed by Davaine, and in the decade from 1850-1860 the presence of these organisms in anthrax blood was testified to by a number of observers. In the year 1860 Delafond found the parasite not only in affected cattle but also in the blood of animals inoculated with material taken from the natural disease, and three years later Davaine, impressed by the work of Pasteur on fermentation, carried out still more convincing experiments. Side by side he inoculated animals with blood containing the bacteria and blood free from them, observing the development of anthrax only in those animals which had received the material containing the organism. Nevertheless, in all these experiments, some virus in the blood and not the organisms visible under the microscope might be the cause of the disease. The proof that the bacteria seen first by Pollender and Davaine were the infectious agent of splenic fever had not yet been brought and could not be brought until the organism was cultivated artificially outside the animal body, and successful inoculations carried out with such a culture freed from any virus or poison.

The first attempt to devise a method for the separation of microorganisms from mixtures is probably seen in the experiments of Hallier in 1866. His apparatus, however, did not permit the isolation of individual species, and so many different kinds of organisms appeared that Hallier was led to the doctrine of *pleomorphism,* the doctrine that microorganisms could change their size and shape, developing one into another. Faulty as was the method of Hallier and wrong as were his conclusions, he nevertheless again drew attention to the occurence of bacteria in various pathological conditions as in measles, syphilis, gonorrhœa, glanders and diphtheria. The presence of bacteria in morbid processes was about this time further demonstrated by some of the most reliable investigators of the day, among whom must be mentioned Weigert, Cohn, Oertel, Eberth, Klebs, Rindfleisch, von Recklinghausen and Waldeyer. In most of the observations at this time, however, various cells, cellular detritus of organic and inorganic nature, particles of fat and different crystals were grouped together as living organisms. In 1871 von Recklinghausen found, in the organs and tissues of individuals dead of pyæmia, puerperal fever, typhoid fever, and rheumatism, small bodies with a definite structure which were not dissolved by alkalies, by acetic acid or by glycerine. Such bodies were clearly organic in nature. During the same year Waldeyer demonstrated aggregations of minute forms which were evidently bacteria, in the heart muscle in pyæmia and in the pelvis of the kidney in pyelonephritis, and a little later Weigert found bodies with the reaction described by von Recklinghausen in the corium in cases of hemorrhagic smallpox. Klebs also in 1870-1871 described his *microsporon septicum* in gun-shot wounds, in granulation tissue, in fistulæ, in diseased bone-marrow, in the cartilages of the joints in arthritis, and in diphtheria. He devised methods for the isolation of organisms in pure culture, the so-called fractional cultivation, but had no success. The observations of so many competent observers that bacteria were constantly present in diseased conditions coupled with the failure to demonstrate organisms in the normal tissues, could best be explained on the theory that they were the cause of the pathological change. The whole question was involved in great obscurity, however, since no proof had been brought that any particular variety of organism seen with the microscope was derived from a previously existing organism of the same size and shape and with the same properties. The obscurity was rendered more dense moreover by the contentions of such observers as Bilroth and Klebs, that the same microorganism could be the cause of the most diverse pathological conditions, pyæmia, septicæmia, puerperal fever, phthisis, smallpox, diphtheria, and cholera. The etiology of infections could only be cleared up by the demonstration of specific differences in the many bacterial forms found in diseased organs and tissues.

About this time the Botanical Institute of Ferdinand Cohn in Breslau became the seat of active and illuminating investigations upon microorganisms. The *Monas prodigiosus* had previously been discovered in a red discoloration on food by Ehrenberg and its cultivation accomplished by Fresenius and Erdmann on potato. The pigment produced by this organism enabled the observer to follow the growth from generation to generation, and cast aside as contaminations all those colonies

lacking the red color. Schroeder now cultivated the "prodigiosus" and a number of other pigmented bacteria on a variety of media in Cohn's Institute. He was unable to separate mixtures of organisms into their constituent elements, however, and in consequence could not be sure his colonies did not contain extraneous species having the same morphology as the microorganism which produced the pigment. The crying necessity was for a method which would bring about the separation of one organism from another and enable the observer to test the properties of isolated species. No one appreciated this necessity more than Cohn himself, who clearly saw that until the different bacteria could be isolated, in pure culture, and observed over long periods of time, no certainty could exist as to the origin of any one particular organism from a pre-existing organism of the same size and shape. Nevertheless, on the ground of the various investigations relating to the morphology and the physiological properties of bacteria, Cohn was thoroughly convinced of the correctness of the doctrine that different species of microorganisms existed in nature, differing from each other in form, in biological reactions, and in fermentative activity. The proof for this thesis, which Cohn regarded as the key-note to the whole science of bacteriology, had not yet been brought. Cohn had himself discovered the sporulation in the bacilli and had predicted that spores would be found in the organism of splenic fever. As he himself tells us, he was greatly delighted to receive a letter on April 22, 1876, from a young country physician in Wollstein, Robert Koch, stating that he had succeeded in working out the complete life-history of the anthrax bacillus and that the nature and distribution of the disease could be fully explained by the mode in which the organisms developed and especially by their sporulation, the sporulation which Cohn had predicted and which he himself had observed under the microscope. Koch expressed his willingness to carry out the necessary experiments to prove these claims in Cohn's own Institute and his desire to obtain Cohn's judgment of their value. Cohn at once invited Koch to come to Breslau and on April 30, 1876, Koch, began a three-day demonstration before Cohn in the Botanical Institute. He brought with him many of his preparations and carried out a number of fundamental experiments. He showed Cohn how he could cultivate the anthrax bacillus in sterile blood serum or in the aqueous humor of a bullock's eyes, and how it went through a definite phase of development. During the course of this development the short rods originally present in the blood of animals dead of splenic fever grew out into long threads or chains of bacilli in each of which a spore appeared. These spores became free from the organisms which disintegrated and disappeared, and under proper conditions of temperature and moisture underwent certain peculiar changes. As a result of these changes, projecting from each spore there appeared the short rod, characteristic of the bacillus of anthrax as observed in the blood of infected animals. Thus the complete life cycle of the anthrax bacillus was established, the first complete life cycle to be described for any of the bacteria. Koch further showed Cohn how the inoculation of animals always resulted in artificial anthrax when the material employed contained the bacillus or its spores, and only under these conditions, actually inoculating frogs, mice, and rabbits with infectious material in Cohn's presence. He finally proved to Cohn that the nature and the distribution of the disease could be amply explained by the facts which he had brought to light in regard to the life history of the anthrax bacillus. This demonstration took place in the presence of a number of professors in the University of Breslau besides Cohn, notably the physiologist Leopold Auerbach, the pathologist Julius Cohnheim and his assistant Karl Weigert, and Messrs. Eidam, Lichtheim and Traube. It is said that Cohnheim was so astonished and delighted by Koch and his work that he rushed back to the Pathological Institute, called his assistants together and told them to stop their work and hasten to the Botanical Laboratory where they could see the demonstration for themselves. He said Koch had made a startling discovery which in the simplicity and exactness of the methods employed was the more to be wondered at since he was shut off in his life from all scientific intercourse, and yet everything he had done was absolutely original and absolutely complete. "It leaves nothing more to be proved," said Cohnheim. "I regard it as the greatest discovery that has ever been made with bacteria, and I believe that this is not the first time that this young Robert Koch will surprise and shame us by the brilliancy of his investigations." *

The work on anthrax was published almost immediately in Cohn's *Beiträge zur Biologie der Pflanzen* in July, 1876. In a paper of over forty pages Koch describes with great exactness the many experiments he had conducted with the organisms of splenic fever, the methods he had employed and the conclusions which could be drawn from his work. Not only was the sporulation of the anthrax bacillus proven and its life cycle worked out, but for the first time in the history of bacteriology a pathogenic microorganism was cultivated artificially in pure culture outside the animal body and the specific disease produced. This Koch accomplished by the use of hanging drops of aqueous humor or sterile blood serum placed over hollow-ground slides. In these preparations he watched the development of the organisms for a number of generations throwing out as contaminations all those preparations which showed anything besides the characteristic bacillus or its spores. He made a careful study of the natural disease in cattle, sheep and horses, and produced the disease artificially in mice, guinea pigs, and rabbits by inoculation with blood or with splenic pulp from infected animals. He now produced the same disease in these animals by the use of his pure cultures grown for a number of generations outside the body. He thus settled absolutely the etiological relationship of the bacillus of anthrax to the disease and answered the arguments of those who maintained that some virus or poison in the blood and not the or-

* Dr. W. H. Welch was working in Cohnheim's laboratory at this time and states that Cohnheim's enthusiasm over Koch's discovery made a profound impression upon all the men in the Pathological Institute.

ganisms of Pollender and Davaine were the infectious agent. In addition to his production of anthrax in mice, guinea pigs and rabbits, Koch inoculated dogs and two varieties of birds, namely, partridges and sparrows and noted their resistance to infection. The same insusceptibility he found also in frogs and in his examination of the tissues of these animals, called attention to the remarkable fact that the anthrax bacilli were ingested by the white corpuscles of the blood. A similar ingestion of the organisms by blood cells he notes in material taken from the spleen of a horse dead of anthrax.

This paper is one of the great classics in bacteriology. By it the first clear light was thrown upon the dim obscurity which enveloped the world of microorganisms. By it the path was first shown along which the growth of this science was to move. It is significant that in the thirty-five years which have passed since the publication of this first paper of Koch's on anthrax, the world-wide development of bacteriology has not thrown doubt upon the accuracy of Koch's observations, nor disproved any of the conclusions which he drew. Indeed but little of importance has been added to the facts which Koch established concerning the life history of the anthrax bacillus and the etiology of splenic fever. In November of the following year, 1877, Koch published his second paper. Here he described his method for making films of bacteria on the surface of coverslips, fixing them by drying or gentle heat, and his application of Weigert's use of the aniline dyes for the demonstration of bacteria in tissues, to the study of these bacterial films. In addition to the method of staining the bodies of the bacterial cells Koch also devised a method for staining the flagella on some of the motile forms. Cilia had previously been seen on bacteria, but now for the first time satisfactory proof of their existence was brought. The bulk of this paper, however, is given up to the subject of the photography of bacteria, in which Koch was keenly interested because of his belief that only by carefully prepared photographs could different observers compare their findings and avoid the many erroneous impressions resulting from imperfect descriptions of microscopic forms.

The work on anthrax was accepted everywhere in Germany, but met with much opposition in France at the hands of the physiologist Paul Bert. Bert maintained that every disease must be caused by a virus of the nature of an organized ferment whose activity was inhibited by oxygen. Since the anthrax bacillus could develop in the presence of oxygen, it could not be the virus which produced the disease. Bert's opposition to Koch's conclusions led the great Pasteur into the study of anthrax and into the field of infectious diseases, where as he himself said at the time "he had thus far been a stranger." Pasteur confirmed all of Koch's observations and completely overwhelmed Bert with the force of his arguments.

The study of anthrax, however, started Pasteur upon the study of other infectious conditions and in the course of his experiments he found an organism which was the cause of a septicæmia in animals, to which he gave the name *vibrion septique*. The septicæmia produced by the *vibrion septique* was entirely different from the septicæmia produced by the organism of splenic fever. As a result of Pasteur's work on anthrax and on the septicæmia due to his *vibrion septique* his mind was again turned to the relation between fermentation and disease and we find him on April 30, 1878, in collaboration with Joubert and Chamberland advocating publicly the old doctrine of the dependence of disease upon the growth of microorganisms within the body. Even before that time, however, Koch had been putting this theory to a practical test, studying with great minuteness the various effects which were produced in animals by inoculation with all sorts of putrid material. The results obtained by Koch were also published in 1878 in a paper entitled, *Untersuchungen über die Aetiologie der Wundinfektionskrankheiten,* which constitutes the third of his important publications. In this paper Koch puts forward clearly the exact state of knowledge on the subject of surgical infections; he explains the difficulties which had to be overcome in working out their etiology and describes the results which others before him had achieved. He then states that he determined to study especially analogous conditions in animals resulting from the subcutaneous introduction of material from various sources. He tells how he succeeded in artificially producing conditions which were strictly comparable to surgical wound infections and how these infections in animals were always due to microorganisms. He reports six different kinds of infection so produced, pictures the organism associated with each, describes in detail the appearances of the organs and tissues of the infected animals. He notes the fact that certain species are susceptible to one kind of microorganism, other species to other kinds, points out that the animal body itself is the very best medium in which to obtain *pure cultures* and that the pure cultures so obtained can be kept alive by the continuous inoculation of fresh animals. No greater proof that infectious material consists of different kinds of living microorganisms capable of indefinite multiplication could be asked, except the cultivation of the organisms in pure culture outside the animal body and the production of the lesions by the organisms themselves. This proof had already been furnished by Koch for anthrax. Several improvements in bacteriological technique were also described by Koch in this paper, the most important being the adoption of the oil-immersion lens of Stephenson and the Abbe condenser for the study of microscopic forms.

Koch's growing reputation prevented his longer sojourn in Wollstein and the impression which his experiments and personality had made on Ferdinand Cohn and the other men in Breslau led them to procure a place for him there as *Gerichtsarzt* or Municipal Physician. In the summer of 1879 Koch moved his family to Breslau and took up the work of the new position. The strenuous life of a city practitioner proved little to Koch's liking, the salary of the new position was much below that required for himself and his family and possibly too he found that his scientific work was interfered with. At any rate after three months sojourn in Breslau he retraced his steps to Wollstein where his old place was still unfilled and

where it is said he was received with wild jubilees by the local populace. Koch, however, was now much too big a man for this little community. About this time Finkelnberg, one of the members of the *Gesundheitsamt* in Berlin, resigned to accept a professorship and Koch, largely through the instrumentality of Cohnheim, was selected as his successor. He moved his family to Berlin and from this time on devoted himself exclusively to laboratory work. At the time he entered the *Gesundheitsamt* bacteriological investigation, which had previously been carried out there with some zeal, was largely abandoned. With characteristic energy Koch gathered about himself a number of assistants and students and with their help improved and applied the methods and technique which he previously had devised. At the end of the first year the observations were published in the *Mittheilungen aus dem kaiserlichen Gesundheitsamte* for 1881. In this volume among other articles were three papers by Koch alone, one by Koch and Wolfhügel and one by Koch, Gaffky and Loeffler, all contributions of the greatest importance to the now rapidly developing science of bacteriology. Many of the methods for sterilization and disinfection which are now in vogue were devised at this time and many great improvements in bacteriological technique were introduced. In the first paper in this volume Koch described what we must regard as his greatest achievement, his poured-plate method for the isolation of organisms in pure culture. Up to this time no method had ever been devised for obtaining pure cultures of organisms from mixtures. We know that Koch had pure cultures of the anthrax bacillus, for in this work he first obtained the organisms from the blood of an infected animal, using the greatest precautions to prevent contamination, and employing carefully sterilized instruments, sterilized slides and coverslips. In addition he actually watched the development of the bacteria under the microscope, casting aside as worthless any preparations which showed extraneous organisms and controlling his work by constantly producing the disease by inoculation. We know also that he recognized the value of the animal body as a medium in which to obtain pure cultures of bacteria and in his work on wound infections showed how one organism would develop exclusively in one animal, another organism in another. This was entirely a different matter, however, from obtaining pure cultures from mixtures. No scheme had yet been hit upon, no apparatus had been invented by means of which this could be accomplished. Attempts to solve the problem had been countless and the difficulty of solving it is apparent when it is recalled that such skillful investigators as Hallier, Klebs, Lister, Naegeli, Salamonson and Buchner had all devised apparatus and methods for this purpose, but had failed to meet with success. Koch in order to obtain pure cultures made use of nutrient gelatin. This material had previously been employed in the cultivation of microorganisms, but only in solutions so dilute as not to harden and furnish the firm transparent medium Koch desired for the study of his colonies. Koch now used the gelatin in such proportions as to give a solid coagulum when cooled, and added to this gelatin meat infusion with which to furnish the microorganisms the substances necessary for their nutrition. In his previous work Koch had observed that if a slice of potato was sterilized by cooking and kept under aseptic precautions in closed and sterilized vessels, no growth of any sort or description appeared upon the cut surface. If a similar slice of potato was exposed to the air for a few minutes and then put in a warm chamber, after a few days its surface was covered by colonies of various colors, which when examined microscopically were found to be made up each of its own kind of microorganism. Acting upon this idea Koch spread his newly devised gelatin upon the surface of sterile glass slides or dishes and inoculated the surface by drawing over it a platinum wire which after sterilization had been immersed in the mixture of bacteria to be studied. He now found that isolated colonies developed along the line of these streaks and that these colonies were each composed of but one kind of microorganism. He next further improved this method by inoculating the melted gelatin directly, shaking it well to get a separation of the individual cells and pouring this over the surface of a sterilized glass dish. This method of making streak cultures and of pouring plates gave pure cultures and solved the problem which had been attempted by so many of his predecessors, the problem which the scientific world recognized had to be solved before the science of bacteriology could advance very far beyond the place where it had rested for so many years.

Simple as the poured-plate method appears to us at the present time and clear as are the various steps taken by Koch in the solution of the difficulty, it still remains to us the only practical procedure for obtaining pure cultures of microorganisms, the slight modifications which it has undergone in the quarter of a century since its discovery relating largely to the composition of the medium which is employed. For us in America it is interesting to note that the only real improvement over Koch's poured-plate method came from the hands of an American investigator, Professor Barbour, who has devised an ingenious apparatus by means of which he can obtain cultures from isolated bacterial cells. From the difficulty of using this method, however, it can have but a limited application in bacteriology.

The end of the year 1881 may be said to mark the close of the inventive or constructive period in Koch's life. In the decade from 1872, when he returned from the Franco-Prussian war, to the year 1882 the science of bacteriology had changed from a chaos of conflicting views and observations to a well ordered system. The methods for fixing and staining bacteria so as to make their microscopic study possible had been devised, their cilia had been stained, the oil-immersion lens and the Abbe condenser had been utilized, a method of separating single species from mixtures had been found, the pathogenic bacteria had been cultivated in pure culture, the etiology of infections had been cleared up, the germ theory of disease had become a proven doctrine. For most of this advance in knowledge Koch was himself responsible.

From this time on the work of Koch and his pupils was

largely the application of the methods already perfected to the study of other conditions and the next few years were rife with epoch-making discoveries in the field of infectious diseases. As he himself said, when once the right method was found, the solutions of the problem came to their hands as easily as ripe apples fell from the trees. It was the method which was essential. It was the method which Koch had looked for. It was the method which he had found.

In 1882 Koch worked out the etiology of tuberculosis by his discovery of the tubercle bacillus. To do this he devised a new method of staining by means of which he could differentiate between the organisms always present in tuberculous lesions, and those accidentially found there, finally succeeding in cultivating the organisms he had stained on solidified blood serum, and proving their relation to the disease by inoculation experiments. The preliminary report of this work appeared in 1882 in the *Berliner klinische Wochenschrift,* the full account of the many experiments being published in 1884 in the second volume of *Mittheilungen aus dem kaiserlichen Gesundheitsamte.* The main points in the life history of the tubercle bacillus, its relation to tuberculosis and the methods which should logically be adopted to prevent the spread of this disease were presented with great clarity and not only are these publications of Koch's models for future generations of scientists, but the practical importance of the knowledge furnished the world by Koch at this time can hardly be overestimated. In reading these papers it is interesting to note that in his early work Koch held certain ideas which could not later be substantiated. Thus he believed that the small highly refractile bodies seen in the tubercle bacillus were spores, a point of view not subsequently confirmed. He also taught that tuberculosis of man and of animals was identical and due to the same bacillus, and that the bovine disease was a source of great danger to the human race, and was to be treated like other diseases of animals transmissible to man. As is well known this opinion was greatly modified by Koch himself in his later work.

In this communication Koch seems for the first time to have clearly formulated in print the laws which go by the name of "Koch's postulates," although he evidently made use of these postulates in verbal communications before this period. In a later address entitled *Ueber bakteriologische Forschung* which Koch delivered before the International Medical Congress in Berlin in 1890, we find the fullest and most satisfactory exposition of these laws. According to these postulates a parasite to be regarded as the cause of a disease must fulfill certain conditions. First, it must be found in every case of the disease, and under conditions which explain the pathological changes and the clinical symptoms. Secondly, it must not be found as an accidental and harmless parasite in other diseases. Thirdly, after isolation from the body and cultivation in pure culture, it must have the ability to produce the disease. When these conditions are fulfilled then no other relation between the parasite and the disease can be imagined than that the parasite is the cause of the disease.

In 1883 Koch was made the head of the German Cholera Commission and went first to Egypt and then to India. In a painstaking investigation of Asiatic cholera, both in patients and in the post mortem room, he not only established many new points concerning the pathology of the infection, but isolated the cholera vibrio and brought forth convincing proof of its etiological relationship. Of especial importance from the public health standpoint was his cultivation of the vibrio from drinking water and from articles of food. The possibility of contact infection in this disease was not overlooked by Koch and some of his earliest work demonstrated the presence of the living vibrios on the clothing of patients. On Koch's return from India he was given a donation of 100,000 marks by the State and Kaiser Wilhelm I bestowed upon him the Order of the Crown, second class.

In 1885 Koch left the *Gesundheitsamt* and became Professor of Hygiene and Bacteriology in the University of Berlin, a chair with this title being made for him. Both at the *Gesundheitsamt,* and later at the University his laboratories were crowded with men from all over the world anxious to learn the new methods and technique. England, America, France and Italy were well represented but German physicians flocked to him especially, many of them to take the course in Cholera Diagnosis which he offered at the *Gesundheitsamt,* this being required by the Government of the official medical men who were stationed on the frontier. In the list of students who worked with Koch or took the courses offered in his laboratory are many of the foremost investigators of the present day, included among the number being Gaffky, Loeffler, Hueppe, Wolfhügel, Esmarck, Behring, Flügge, Pfeiffer, Gärtner, Fisher, Wassermann, Froboenius, Kolle, Carl Fraenkel, Hesse, Weiss and Kossel in Germany; Welch, Prudden, Abbott, Vaughan, Novy, Biggs, Laplace, Archinard, Ernst and Shakespeare in this country. But three among these last named, however, actually worked under Koch himself, Dr. Welch and Dr. Prudden and later Dr. Ernst, at the Hygenic Laboratory of the University.

It is significant that the etiology of many if not the majority of the infectious diseases which we now understand was solved by Koch or his pupils. Thus to Koch himself must we credit anthrax, tuberculosis, cholera, infectious conjunctivitis; to Gaffky, typhoid fever; to Loeffler, diphtheria and glanders; to Pfeiffer, influenza; to Kitasato, tetanus, symptomatic anthrax, and bubonic plague in part. In many other instances the methods which Koch devised, when adopted by his followers all over the world, have brought solution to problems of the greatest importance in medicine and surgery.

It is interesting to us at Johns Hopkins that Dr. Welch came directly from his studies in Berlin, where he was a personal student of Koch at the University and took Koch's first course in bacteriology, to Baltimore when the pathological laboratory of the Johns Hopkins Hospital was opened. He brought with him cultures of a number of microorganisms and at once gave courses in bacteriology similar to those given in Berlin. Our laboratory is thus one of the first if not

actually the first laboratory in America where modern bacteriological technique was adopted, and to Dr. Welch more than to any one else American medicine is indebted for the introduction of the Koch methods.

The establishment of the Saranac laboratory for the study of tuberculosis by Dr. Trudeau may also be regarded as the direct outcome of Koch's first paper on tuberculosis published in 1882.

In 1890 Koch described the preparation of tuberculin which was immediately heralded about the world as the great specific for tuberculosis. Its failure to become this specific is the one blot on Koch's reputation. As Trudeau so clearly points out, Koch in his first investigation on this remedy departs for the only time in his life from the rigid methods which he previously and subsequently applied to all his work. Careful examination of Koch's original publication on tuberculin leaves little doubt that Koch was himself thoroughly convinced that it was a great healing remedy for early cases of tuberculosis of the lung. Why it was that he did not demand of himself the rigid proof for his statements which he knew others would at once demand of him will always remain a mystery. Of what other man of science can it be said, however, that during a life-activity of forty years but one of the many important conclusions which he drew from his work could not be subsequently confirmed?

In 1891 Koch became Director of the *Institut für Infectionskrankheiten* in Berlin which was built under his special direction. Here he remained as Director till 1904 when he was relieved at his own request, his place being taken by his former pupil Gaffky. From 1904 till his death he was *Ehrenmitglied* or Honorary member of the Institute and continued there his active investigations. The Institute, like the Hygienic Laboratory of the University and the *Gesundheitsamt*, in its turn became the Mecca for native and foreign students. Koch gathered about himself a number of the foremost investigators in Germany who attracted to themselves men from various parts of the world. Wassermann, one of the ablest of Koch's assistants, has been especially friendly to Americans and a number of Johns Hopkins graduates have worked with him, thus coming indirectly under Koch's influence. Among others in this country who worked in the Institute may be mentioned: Strong, Ford, Cole, Moss, Jobbling and Mitchel.

During the period when Koch served as Director of the Institute he was constantly engaged in the study of the infectious diseases and was especially concerned with the problem of devising the proper measures to limit their spread. The procedures adopted at the time of the great cholera epidemic in Hamburg in 1892 were largely the result of his discoveries. The following year he made further important contributions to our knowledge of this disease and pointed out how clearly many of the great epidemics could be traced to polluted water, advocating water filtration as the best means of preventing its spread by this path.*

* The method of cultivating cholera vibrios from the dejecta by the use of the Dunham's solution of peptone and salt was first employed by Professor Dunbar of the Hygienic Institute of Hamburg, who was also the first to cultivate the organism from the dejecta of individuals with no symptoms of the disease. In connection with this the following papers should be consulted: Koch, Ztschr. f. Hyg. u. Infectionskrankh., 1893, xiv, 326; Dunham, *Do.*, 1887, II, 337; Koch, Berl. klin. Wchnschr., 1893, xxx, 1; Gaffky, Arb. a. d. Gsndhtsamte., Berl., 1896, x, 110.

Koch never took a narrow view in regard to the etiology of infectious diseases and in his earliest publication calls attention to the possibility that protozoa as well as bacteria may be the cause of disease in man. In 1896 at the behest of the English Government he went to South Africa and Cape Colony to study rinderpest. He devised a method of preventive inoculation to control this disease and spent some time there in the study of protozoan parasites. Upon his return to Berlin he published the results of his investigations upon Texas fever, tropical malaria, black-water fever, surra, and also upon rinderpest and bubonic plague. He was particularly interested in the study of malaria and spent some time in Italy in 1898 investigating the disease in that country.

In 1900 Koch gave his famous London address on tuberculosis, in which he modified the views orginally expressed as to the identity of bovine and human tuberculosis and maintained that no great danger exists of the transmission of the animal disease to man. In combating the disease, the greatest emphasis, he said, should be laid upon preventing the direct spread of tuberculous infection from people suffering from the disease, particularly in its active form. A storm of criticism arose but rapidly abated when the various investigations which this address stimulated revealed that most cases of human tuberculosis show the human type of the tubercle bacillus and not the bovine type. While the amount of bovine tuberculosis in children is probably greater than was admitted by Koch in 1900 the decade which has passed has served only to demonstrate the correctness of Koch's view that our greatest efforts should be directed towards preventing infection from pre-existing cases of human tuberculosis.

In 1902 Koch made a trip to German East Africa on behalf of the German Government, to engage in the study of the *Küstenfieber der Rinder*, and on his return published important observations upon this disease and upon recurrent fever and trypanosomiasis. About this time also he began his campaign against typhoid fever in southwest Germany, establishing new principles according to which this disease is to be controlled. The ideas which Koch promulgated at this time in regard to this infection have been adopted in nearly all civilized countries where typhoid fever exists.

In 1905 Koch was one of the recipients of the Nobel Prizes and in 1906 he headed the Sleeping Sickness Commission and with the members of this Commission went to German East Africa, to English Central Africa and to the Victoria Nyanza. At this time he introduced the use of atoxyl in sleeping sickness. In the following year Koch came to America and took part in the International Tuberculosis Congress held in Washington in that year. On his return to Berlin he was made a member of the Academy of Sciences and was given the title *Excellenz* by the present German Emperor.

The latter part of Koch's life it seems to me is extremely

sad. Bitterly disappointed as he must have been in the failure of tuberculin to become the great healing remedy he had clearly expected it would be, adopting in his family life a course of conduct which alienated him from many of his friends and apparently robbed him for some time of some of those official honors which his scientific attainments had merited so long, gradually losing his strength and suffering from infirmities which a life-long devotion to science had brought on, Koch seems a somewhat pitiable figure. He was indeed deprived of that peaceful and honorable old age which the people of his race so dearly love. Throughout this period of Koch's life he carried himself with the greatest dignity of character, indifferent to the criticisms which were heaped upon his private life, just as previously he had been indifferent to the strictures which were passed upon his scientific work. In March, 1910, he began to suffer from cardiac distress, but refused to give up his work at the Institute, where he labored daily from nine in the morning till half-past two in the afternoon. On April 7 he lectured on the Epidemiology of Tuberculosis before the Berlin Academy of Sciences, his address on this occasion being published some months after his death in the *Zeitschrift für Hygiene* which he and Flügge had founded.

On April 9 he had a sudden attack of heart failure in the night and was saved only by the use of the strongest stimulants. Under the untiring care of his former colleague and devoted friend, Dr. Brieger, he gradually improved a little in strength and health, but he knew the end had come and he estimated with scientific accuracy the number of days and hours he was likely to survive. His strength, however, was somewhat greater than either he or his physicians had anticipated and he recovered sufficiently to sit up in a wheeled chair and receive the visits of his devoted friends. In his modest apartments surrounded by his collections of minerals, plants and animals, his chief delight was talk of the science to which his life had been devoted. His failing faculties could always be roused by the slightest reference to new ideas in bacteriology even when his failing will power could hardly concentrate his attention upon the events of this life. His strength revived sufficiently for him to be removed to Baden-Baden, where it was hoped that the clear balmy air might assist his recovery, but his race had been run and he died Friday, May 27, in the 67th year of his age. Like his great master, Goethe, whose precepts he had followed from his youth up, Robert Koch met death face to face.

His body was cremated on the following Monday, and his ashes now rest in the Institute founded for him in Berlin in a special room where also are deposited the various medals and orders bestowed by a devoted people upon one of the greatest, if not the greatest, of her many sons whose lives have been devoted to the study of the medical sciences.

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In preparing this account of Koch and his work I am particularly indebted to a short life of him which was written by W. Becher and was published in 1891 in Berlin, entitled *Robert Koch, Eine biographische Studie.* In the historical development of the subject frequent reference was made to Loeffler's *Vorlesungen über die geschichtliche Entwickelung der Lehre von den Bakterien,*" Leipzig, 1887. During the past year a number of important biographical notices of Koch have appeared in the current literature and among them are especially to be noted a note by Ehrlich in the *Zeitschrift für Immunitätsforschung und experimentelle Therapie. Originale.* 1910, Bd. VI., Heft 1; an address by Gaffky in the *Deutsche medicinische Wochenschrift,* 1910, No. 50, s. 2321; a paper by C. Fraenkel in the *Münchener medicinische Wochenschrift,* 1910, No. 25, s. 1345, and one by Trudeau in the *Journal of the Outdoor Life,* 1910, July, p. 189. The enormous activity of Robert Koch is indicated by the many papers which he published. The following list includes the most important of his scientific contributions, but is in no sense to be regarded as a complete record of his writings:

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ROBERT KOCH.*

(December 11, 1843 - May 27, 1910.)

THE FATHER OF THE MODERN SCIENCE OF TUBERCULOSIS.

By S. ADOLPHUS KNOPF, M. D.,
Professor of Phthisiotherapy at the New York Post-Graduate Medical School and Hospital.

For the privilege of being with you here to-night and of joining in the tribute which this Society, founded for the study of tuberculosis, is to pay to the lately departed master of the modern science of tuberculosis, I feel profoundly grateful. We who are outside of the justly celebrated Johns Hopkins Medical School look upon it as a Mecca to which a pilgrimage means hearing and seeing the best that exists in modern medical science, and for this reason I feel all the more glad to be with you and much honored by the invitation extended to me by the officers and members of this Society.

With all your eagerness for the study of the latest things which may help to throw light on unsolved medical problems or relieve human sufferings, you remain true to the tradition established by the two most distinguished founders of the medical department of this great university, Professors Osler and Welch, in that you do not neglect the historical study of medicine and, whenever occasion presents itself, you pay tribute to the pathfinders or heroes in our beloved profession. By naming this society the "Lænnec" you honored one who was perhaps the greatest savant in the science of tuberculosis of his day, the immortal René Théophile Hyacinthe Lænnec (February 17, 1781–August 13, 1826). It was he who taught us so much about the tubercle as the characteristic macroscopic evidence of tuberculosis and who invented for us the stethoscope, that valuable instrument almost indispensable in the diagnosis of pulmonary and cardiac diseases.

To-night you are here under the auspices of this society to honor the memory of one whom I believe we can justly call the father of the modern science of tuberculosis. The officers of this society have graciously assigned to me the task of speaking on Robert Koch's achievements regarding tuberculosis.

Koch's brilliant career as father of the modern science of tuberculosis began, of course, on that memorable evening of the 24th of March, 1882, when he gave to the world the result of his painstaking work. It was the usual monthly meeting of the Physiological Society of Berlin, but it was perhaps the largest gathering which that body ever had. Koch's paper was announced under the title, "The Etiology of Tuberculosis." Taking into consideration what Koch had given to science before along the same lines (I refer to the discovery of the spores of the anthrax bacillus and his concomitant bacteriological studies), the hearers were, of course, expectant and looked for great things in store for them. It was characteristic of Koch's modesty and true scientific spirit that he had preferred to refrain from talking about his researches in tuberculosis until he could conclusively prove his thesis to the satisfaction of everyone and show absolutely accurate results.

*Address delivered before the Lænnec Society for the Study of Tuberculosis, The Johns Hopkins Hospital, Baltimore, March 27, 1911.

To students of bacteriology it must be recalled that Koch was the first to seek the production of a solid medium for the purpose of getting pure cultures, and it was only after he was in possession of such a medium that he attempted to isolate the germ found in tuberculous tissue.

It is of historical interest that on the evening of March 24, 1882, after Koch had finished reading his paper, there was no applause or any enthusiastic manifestation of approval, and for the first time in the history of that society the paper, though listened to with the most profound and respectful silence, was not discussed. The facts presented by that master of bacteriological science were too convincing for discussion. The audience looked expectantly to that most honored member and veteran debater, father of cellular pathology, the immortal Rudolph Virchow, but he too remained silent. He felt that another great master in medicine had arisen, and that the evidence of Koch's conclusions did not permit any doubt or dispute. The original communication announcing the discovery of the tubercle bacillus as the prime and only cause of tuberculosis appeared in the *Berliner klinische Wochenschrift* of 1882 (No. 15, p. 221). It is a masterpiece of scientific demonstration.

It might be interesting to my young hearers to know that they can get access to an exact reproduction of this paper in the *Zeitschrift für Tuberkulose* of July, 1910 (Band 16, Heft 2). The editors of this periodical very justly stated that a more fitting memorial could not be printed at the time of Koch's death than that important paper which gave rise to all our modern tuberculosis research work and at the same time gave to its author a well-deserved recognition and world-wide reputation.

In his paper Koch did not fail to pay tribute to the works of Villemin, Cohnheim, Salomonsen, Baumgarten and Tappeiner, who had given us conclusive proof that tuberculosis was a transmissible disease, but through Koch—and Koch alone—we have come to know the actual factor of infection and direct cause of all tuberculous diseases. It is he who showed us the presence of the germ in the pulmonary secretions and involved tissues, and also, to a minor degree, in other secretions of man and beast afflicted with tuberculosis. It is because of this knowledge that the new science which we might call the modern prophylaxis of tuberculosis was created.

And now, after a lapse of nearly thirty years since the memorable discovery, we can statistically prove, beyond the shadow of a doubt, that, thanks to the rational, practical yet simple methods of prophylaxis which soon followed the discovery of the bacillus of tuberculosis by Robert Koch, the mortality from tuberculosis has been on a steady decrease in nearly all civilized countries.

When we consider that the present morbidity and mortality from tuberculosis in the countries which have adopted rigorous anti-tuberculosis measures is in some instances two-thirds and in some even one-half what it formerly was, we must also admit that the material wealth which is the gain of thousands of communities, because Koch lived and labored, is beyond human calculation. Our sociologists and economists have estimated the value of a single human life as an economic asset of $5000 to a community. Thus the figures in material gain to the world at large for which this one man is responsible must stagger our imagination. But we as physicians do not look upon life only as representing a financial asset to the community. We come into too close contact with human suffering and sorrow for that. We rather emphasize the value of the discovery of our great Koch by the number of fathers, mothers, wives, husbands and children who were saved from an untimely death. We think of the tears and sorrow, of the anxiety and worry spared to untold numbers; we appreciate the joys and happiness which were preserved to thousands because the great white plague did not enter their homes. And all this preservation of human joy and happiness has been brought about because of one single discovery of Koch and the resulting indication of how to prevent disease.

But this phase of our medical science, which is truly preventive medicine, is not the only one whereby we as physicians and the world at large have been benefited by Koch's discovery. The presence of the bacillus in the sputum gives in doubtful cases a well-nigh irrefutable evidence of tuberculous infection of the respiratory tract.

In the discovery of tuberculin Koch has given us another adjuvant of great value in the diagnosis of tuberculous diseases in man and animal.

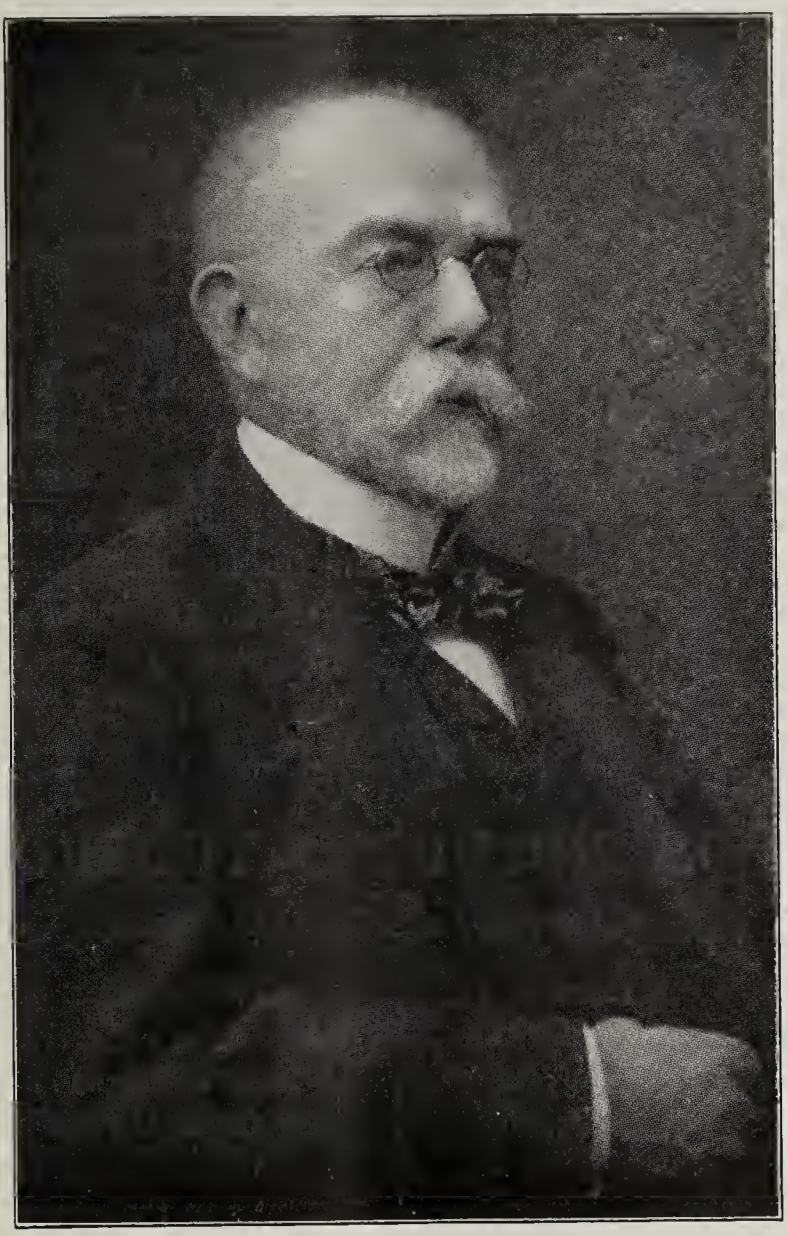
A word regarding tuberculin as a therapeutic product. It is now generally conceded that when in 1890 Koch announced to the world the discovery of tuberculin as a means of curing tuberculosis, he did it against his better judgment, for he felt that he had not experimented with it long enough. The year 1890 was indeed an unhappy one in Koch's brilliant career. The powerful product used in far too large doses by inexperienced men indiscriminately in early and late cases was followed by disastrous results. But time has justified Koch's original claim, and to-day his tuberculin in the hands of careful clinicians has certainly proven to be, in certain cases of tuberculosis, a valuable therapeutic adjuvant.

Koch did not limit his researches to the bacteriological causes of tuberculosis or to the discovery of tuberculin, and it may be a surprise to many to learn what a deep interest he took in the sociological aspect of tuberculosis. He studied all sides of the question—municipal control, popular education, the housing problem, etc. More than once did he express to me personally his approval of Professor Biggs' work in New York relating to the municipal control of tuberculosis, and he also referred to it in his celebrated London address in 1901.

In regard to this communication made before the British Congress, justice requires us to say that Koch's conclusions as to the rarity of the transmission of bovine tuberculosis to human beings were too sweeping, this having been borne out by subsequent investigations. But had it not been for Koch's

London address, much scientific work which has now cleared up the controversy would not have been done.

Koch's last paper, read before the Academy of Sciences of Berlin on April 7, 1910, only about six weeks before his death, and published in the *Zeitschrift für Hygiene und Infektionskrankheiten* October 28, 1910 (Vol. LXVII, No. 1), showed his deep interest in the sociological aspect of tuberculosis. The article was entitled "The Epidemiology of Tuberculosis." In it he very justly ascribes the still very great prevalence of tuberculosis in certain sections of Europe to the unfortunate housing conditions and particularly to the overcrowded sleeping quarters of the masses. He also came to the conclusion that where institutional care had been most readily available, the morbidity and mortality from tuberculosis have been reduced to the greatest extent, and vice-versa.



Koch believed in popular education, and I have received many a kindly word from him to encourage me in my humble labors in that direction. In his last letter to me, a few months before his death, he wrote:

> Popular works on tuberculosis are destined to play an important part in the enlightenment of the people, and the American people seem to be particularly susceptible to such education.

I hope we may deserve this gracious compliment paid to the American people by the great Koch.

And now, in conclusion, a few words on the personal side of this great man. On the evening of the 11th of April, 1908, Koch was the guest of the German Medical Society of New York. It was indeed a distinguished gathering. Professor Karl Beck, as the president of the Society, was the toastmaster of the evening. Your own distinguished teacher, Professor Welch, being one of Koch's first pupils, welcomed the great scientist to our shores, and spoke in eloquent words of the achievements of his master. Equal praises were bestowed upon Koch by the Nestor of the New York and the entire American medical profession, Professor Abraham Jacobi. Andrew Carnegie, the philanthropist, who had given 500,000 marks for the Koch Institute in Berlin, praised Koch as a hero of civilization and peace, far greater than a hero in war, and concluded by saying:

> Every age has its ideals, and the servants and saviors of mankind are our present-day ideals, for I firmly believe that service to mankind is the highest service to God.

And what did the great Koch reply to all this praise and eulogy? His answer was of so inspiring and modest a character that I believe it to be worth while to reproduce it in the original words. I will repeat it here in German as it was delivered, and translate it into English as exactly as possible:

Wenn ich alles zusammenfasse, was hier zu meinem Lobe gethan und gesagt worden ist, und die grosse Auszeichnung, die Sie mir zu Theil werden liessen, in Betracht ziehe, dann entsteht in mir ein Bedenken, ob ich auch wirklich berechtigt bin, mich so feiern zu lassen. Manches von dem, was mir Rühmliches nachgesagt wird, kann ich, wie ich glaube, mit gutem Gewissen akzeptieren. Aber ich habe nichts anders gethan, als was Sie jeden Tag thun, nämlich ich habe gearbeitet was ich konnte und meine Pflicht und Schuldigkeit gethan. Wenn etwas mehr dabei herausgekommen ist, so liegt das daran, dass ich auf meinen Wanderungen durch das medizinische Gebiet auf Strecken stiess, wo das Gold noch auf dem Wege lag. Es gehört allerdings Glück dazu, das Gold von dem Unedlen scheiden zu können; das ist aber kein besonderes Verdienst. Es freut mich besonders, Herrn Carnegie hier zu sehen, dessen hochherzige Spende zur Koch-Stiftung allenthalben einen tiefen Eindruck gemacht hat. Ich möchte Herrn Carnegie meinen bescheidenen aber herzlichen und warmen Dank aussprechen. Die meinen Namen tragende Stiftung ist berufen, grosse Resultate auf dem Gebiete der Erforschung der Tuberkulose zu zeitigen. Während die Gründung von Krankenhäusern und Sanatorien in der Bekämpfung der Tuberkulose von lokaler Bedeutung sind, soll die Koch-Stiftung uns ermöglichen, in das Wesen der Krankheit tief einzudringen, um so Vorteile zu schaffen, die der ganzen Menschheit zu Gute kommen. Herr Carnegie ist für mich die Verkörperung der besten Eigenschaften des Amerikaners. Er hat seinen Blick gerichtet auf die höchsten und edelsten Ziele.

TRANSLATION.

When I now consider the honor you have conferred upon me here this evening, when I consider all that has been said and done in my praise, there arises in my mind a doubt as to whether I am really entitled to such distinction. Some of the kind things which have been said of me I believe I may accept with a clear conscience, but I have done nothing else than what you are doing every day. I have worked as hard as I could and have fulfilled my duty and obligations. If the success really was greater than is usually the case, the reason for it is to be found in the fact that in my wanderings through the medical field I came upon regions where gold was still lying by the wayside. Fortune is necessary to be able to distinguish gold from the base metals, but that is no great merit. I am glad

to see Mr. Carnegie here, whose generous gift to the Koch Foundation in Berlin made everywhere such a deep impression. I would wish to thank Mr. Carnegie with all my heart. The foundation which is to bear my name is, I hope, destined to show great results in the field of tuberculosis research. While special hospitals and sanatoria for the treatment of tuberculosis are of local importance in the combat against tuberculosis, the Koch Institute or Foundation is destined to study the underlying causes and as yet unsolved problems of the disease and thus will benefit mankind at large. Mr. Carnegie is to me the embodiment of all the best qualities of an American. His ideals are the highest and noblest.

Koch had a remarkable genius for research work, yet his aim was always eminently practical and his sympathies genuine and real. By hard work and diligent application he revealed to us the hidden mysteries of disease.

Koch was not privileged to see the foundation for further tuberculosis research work, bearing his name, completed. He died on May 27, 1910, surrounded by devoted pupils and friends. By indubitable right he now takes his place with the Immortals and his name will be handed down through generations to come as one who lived and labored for the good of mankind.

In accordance with Koch's last request, his funeral was of the simplest kind, and as an enthusiastic sanitarian he had directed his body to be cremated. His admirers and pupils gathered the ashes of the beloved master and enshrined them in a mausoleum located in the *Institut für Infektionskrankheiten* in Berlin, of which Koch had been a director for many years.

I venture to say that for generations to come, all physicians and likewise the many men and women outside of the profession who are interested in scientific or preventive medicine will, on visiting Berlin, deem it a pious duty to make a pilgrimage to this last resting-place of the ashes of Robert Koch.

When Professor Koch wrote me the last time he honored me by sending his photograph taken a short time before he fell ill. This picture is considered by all who knew Koch one of his best. He graced it with his signature dated February 9, 1910. In availing myself of the permission granted to me to present you with an enlarged reproduction, I beg you to accept it from one of the thousands of humble disciples of the great master as a feeble tribute to him and as a token of esteem for the officers and members of your society.

Let this portrait, which shall henceforth grace the walls of this great university, this likeness of a prince of science, a teacher of teachers, one of the greatest physicians of his time, remind present and future members of the Lænnec Society and all the students of this great university of Koch's motto in life: *Nunquam otiosus* (Never be idle). Let it be to all of us, to you and to me, an inspiration, an incentive to work and a reminder of the fact that though much has been done, there is still more to do.

THE BLOOD PICTURE IN TUBERCULOSIS.

By Margaret Reed Lewis, Baltimore.

The fact has long been established that a cell reacts to its environment and that the condition of any cell at any one time depends upon its environment. The assumption that the cells of the blood would react to the condition of the plasma, might have been made, but it was not until 1896 that Holmes first called attention to the fact that there is a definite relationship between the state of the leucocyte of the blood and the progress of the disease in tuberculosis. Holmes studied the entire cell and while he perceived the metabolic changes of the leucocytes as shown by their granules and even in some cases mentions the condition of the nucleus, he did not observe that there is a definite relationship between the state of the nucleus and the condition of the cell.

To quote Holmes, "A careful study of 100 cases of tuberculosis has shown conclusively that the laws, which bring about disintegration in a tuberculosis patient, bring about the same process at an earlier date in tubercular leucocytes. In these cases, I have found a marked disintegration going on in all varieties of leucocytes and a great decrease in the number of young cells. The tissue forming power of these cells is imperfect. Many of the young cells present is a good sign of reeuperative power on the part of the patient."

The relationship between the state of the nucleus and the metabolic processes of the cell has been investigated by many observers as for instance, Korschelt found that the formation of chitin in insects is associated with nuclear changes. Greenwood found the elaboration of digestive fluids in cells is determined by the nucleus. Maximow found that the secretory granules in the serous cells of the salivary gland originate on the inner surface of the nuclear membrane. Mathews showed that the zymogen granules of the pancreas cells are formed at the expense of nuclear fibrillae. The relationship between the metabolic processes of the cell and the nucleus has not been definitely worked out but the observations of Jacquet, Spitzer, Loeb and R. Lillie seem to demonstrate that the nucleus is especially concerned in the oxydative processes of the cell.

Soon after Holmes' work appeared, Arneth observed that there is a relationship between the state of the nucleus of the neutrophile of the blood and the condition of the patient in tuberculosis. In 1905, Arneth published all his observations upon tuberculosis patients as a monograph, "Die Lungenschwindsucht," in which he states clearly his conclusion in the form of a neutrophilic blood picture, which is adapted for clinical use.

According to Arneth the neutrophile enters the blood as a myeloeyte or at least as a neutrophile having but a single lobe

to the nucleus. As these cells live and mature in the blood, the nucleus becomes divided into several lobes, so that the younger forms have one or two lobes, Arneth calls the lobes "pieces" while the older have four or five pieces. The mature neutrophiles are constantly used up and the younger forms constantly enter the blood, so that if at any time more of the mature forms are used up, it is shown by a larger proportion of the neutrophiles with one or two lobed nuclei than is usually present.

The pieces of the nucleus are of two types, the round piece or "Kernteile," which does not divide again and the bent piece or "Schlingen," which may divide again. Arneth's observations upon human blood show that the neutrophiles can be divided into five classes according to the number of pieces of the nucleus and those classes subdivided according to the kind of pieces in each class, as is seen in the following table.

ARNETH'S BLOOD PICTURE.

NEUTROPHILES.

CLASS I.

Nuclei with 1 round piece (1 Kernteile). Fig. 1.
Nuclei with 1 bent piece (1 Schlingen). Fig. 2.

CLASS II.

Nuclei with 2 round pieces (2 Kernteile). Fig. 3.
Nuclei with 2 bent pieces (2 Schlingen). Fig. 4.
Nuclei with 1 round piece and 1 bent piece (1 Kernteile und 1 Schlingen). Fig. 5.

CLASS III.

Nuclei with 3 round pieces (3 Kernteile). Fig. 6.
Nuclei with 3 bent pieces (3 Schlingen). Fig. 7.
Nuclei with 2 round pieces and 1 bent piece (2 Kernteile und 1 Schlingen). Fig. 8.
Nuclei with 1 round piece and 2 bent pieces (1 Kernteile und 2 Schlingen). Fig. 9.

CLASS IV.

Nuclei with 4 round pieces (4 Kernteile). Fig. 10.
Nuclei with 4 bent pieces (4 Schlingen). Fig. 11.
Nuclei with 3 round pieces and 1 bent piece (3 Kernteile und 1 Schlingen). Fig. 12.
Nuclei with 2 round pieces and 2 bent pieces (2 Kernteile und 2 Schlingen). Fig. 13.
Nuclei with 1 round piece and 3 bent pieces (1 Kernteile und 3 Schlingen). Fig. 14.

CLASS V.

Nuclei with 5 round pieces (5 Kernteile). Fig. 15.
Nuclei with 5 bent pieces (5 Schlingen). Fig. 16.
Nuclei with 4 round pieces and 1 bent piece (4 Kernteile und 1 Schlingen). Fig. 17.
Nuclei with 3 round pieces and 2 bent pieces (3 Kernteile und 2 Schlingen). Fig. 18.
Nuclei with 2 round pieces and 3 bent pieces (2 Kernteile und 3 Schlingen). Fig. 19.
Nuclei with 1 round piece and 4 bent pieces (1 Kernteile und 4 Schlingen). Fig. 20.

For clinical purposes Arneth arranged the various forms found in 100 neutrophiles as a neutrophilic blood picture as follows:

W.B.C.	M.	Class I	Class II	Class III	Class IV
		1K 1S	2K 2S 1K-1S	3K 3S 2K-1S 1K-2S	4K 4S 3K-1S 2K-2S 1K-3S

Class V

5K 5S 4K-1S 3K-2S 2K-3S 1K-4S

Each neutrophile as he observed it was counted under the subdivision of the class in which it belonged; as for instance, a neutrophile with a nucleus as in Fig. 8 would be placed under sub-division 2K1S of Class III. If any myelocytes were observed they would be placed under M as myelocytes or embryonic neutrophiles.

Arneth finds the neutrophilic blood picture of normal persons to be—(the numerous sub-divisions are not quoted in this paper)—:

W.B.C.	M.	Class I	Class II	Class III	Class IV	Class V
8,000	0	5	26	36	28	5

In tuberculosis the older neutrophiles are continually used up and so the large proportion of neutrophiles shifts to the left side of this picture as

W.B.C.	M.	Class I	Class II	Class III	Class IV	Class V
10,000	0	12	48	30	10	0

Then if the patient recovers and so uses up fewer of the older forms, the proportion of neutrophiles again shifts to the right side of the picture. According to Arneth, every case where there is even a slight shifting to the left of the neutrophiles can be diagnosed as tuberculosis, but our observations show that this is probably not so and that other conditions than tuberculosis may give the neutrophilic blood picture with only a slight shifting to the left, so that for diagnosis or prognosis the other blood cells as well as the neutrophiles must be considered.

Investigation was undertaken at the Bellevue Hospital, New York City, under the charge of Dr. J. Alexander Miller, head of the Tuberculosis Out-Patient Department, to determine whether this work of Arneth's was of practical value clinically, especially whether it had any value in regulating the use of tuberculin. In this work over 200 cases were observed with an average of 30 counts on each case. Some of these cases were observed for a period of three years, and on each of these about 100 counts were made.

The division of the neutrophiles into classes according to the lobes of the nucleus sounds simple, but when a number of counts had been made, it was found almost impossible as well as of no especial value to keep to Arneth's sub-divisions, so it was decided to note only the class in which the neutrophile belonged and not the kind of lobes. The threads connecting the lobes of the nucleus are of varying length and thickness and the bending of the lobe to form "Schlingen" is also of varying degrees, so that the decision as to whether a bent lobe shall constitute one lobe or two lobes of the nucleus, will always vary according to the personal equation of each individual investigator. In these observations all bent lobes of the nucleus, where the nuclear bridge was large enough to admit of good nuclear network, Fig. 21, were classed as one lobe, but where the nuclear network is condensed into a coarse thread, Fig. 22, or a fine thread, Fig. 23, they were classed as two lobes. The question as to whether one lobe of the nucleus is on top of another was always decided by careful focussing with a high power. Any very questionable case was not counted. The study of the blood smears, to obtain the neutrophilic blood picture soon showed that changes were to be noted among the other cells of the blood, so a blood picture was made, which would include all the white blood cells, but as no definite change was found in the other cells only the number of each present was noted.

Two hundred neutrophiles were usually counted, never fewer than 100 and the number of the other kind of white blood cells observed while counting these were noted, making a blood picture as follows:

Neutrophiles of Class I, Class II, Class III, Class IV, Class V. Large Lymphocytes. Small Lymphocytes. Eosinophiles, Basophiles and the number of white blood cells. Smears from the blood of a normal person give a blood picture as follows:

Class I	II	III	IV	V	L.L.	S.L.	E.	B.	W.B.C.
5	22	48	26	5	22	18	1	0	8,000

In case a differential blood count is desired it can easily be computed from the complete blood picture.

Many schemes for an index were devised for tabulation purposes and it was finally decided that the changes in the blood picture would be more clearly shown if the number of neutrophiles in Class I + Class II and one-half of Class III, as compared with the number in one-half of Class III + Class IV + Class V was used as an index. This same index was used in some observations by Bushnell and Treuholtz, which appeared later. In the normal blood picture there is about the same number of neutrophiles on each side, *i. e.*

$$\begin{matrix} 5+22+\tfrac{1}{2}\,42=48 \\ \tfrac{1}{2}\,42+26+5=52 \end{matrix} \quad \text{Index} = 48:52$$

From a study of the neutrophilie blood pictures from over 30 supposedly normal persons, the normal blood pieture was found to be

I	II	III	IV	V	L.L.	S.L.	E.	B.	W.B.C.	Index
5	22	42	26	5	22	18	2	1	8,000	48:52

But the study of these blood pictures showed that a blood picture with an index anywhere between 45:55 and 55:45 may be considered normal.

The index is usually written as the number on the left side in tabulations.

The blood pictures from a few of the tuberculosis patients are given below.

PATIENT A.—A young woman who was clinically considered a favorable case. She has neither gained nor lost, but has seemed to improve slightly under the tuberculin treatment. The blood picture shows an improvement after her return from the country, but she returned to work against advice and soon returned to her earlier condition. This patient died during the late summer of 1909.

Date	1	2	3	4	5	6	L.L.	S.L.	E.	M.	Leuc.	Index	Remarks
1907													
May 6.....	21	41	27	8	2	0	0	0	0	0	.....	75.5	Tuberculin.
May 17....	22	34	30	12	2	0	0	0	0	0	.....	71	
May 20....	28	43	20	9	0	0	0	0	0	..	.....	81	
May 24....	26	41	24	12	2	0	0	0	0	0	.....	79	
May 31....	24	40	27	10	2	0	0	0	0	0	11,000	77.5	
June 7 ...	25	37	20	14	2	0	0	0	0	0	12,000	72	
June 10...	20	31	31	17	1	0	13	18	2	1	11,000	66.5	
June 24...	20	41	28	11	0	0	11	23	3	1	10,000	75	
	Away to country.												
Sept. 31...	8	38	26	22	6	0	17	20	3	2	8,000	59	
Oct. 14....	10	36	39	12	3	0	28	6	2	4	11,200	66.5	
Oct. 18....	16	37	31	12	4	0	12	11	2	3	13.600	68.5	
Oct. 21....	10	37	33	15	5	0	25	16	7	1	10.000	63.5	
Oct. 28....	10	48	31	10	1	0	16	5	4	2	12,600	73.5	
Nov. 1....	9	47	33	6	4	0	18	12	4	1	12,800	72.5	
Nov. 8....	16	33	33	17	1	0	24	4	6	2	10.000	65.5	
Nov. 11...	12	46	32	10	0	0	26	15	6	1	11,000	74	
Nov. 18...	..	..	..	..	..	..	..	..	..	..	10,800	....	
Nov. 22...	..	..	..	..	..	..	..	..	..	..	12.000	....	
Nov. 29...	10	40	31	17	2	0	17	6	5	0	13 200	65.5	
Dec. 2.....	16	41	27	14	2	0	28	2	2	0	12,000	70.5	
Dec. 16....	..	..	..		..	..	..	..	..	..	10,600	....	
1908													
Apr. 3....	14	43	34	9	0	0	18	9	3	1	12,000	74	
Apr. 22....													
May 4.....	23	44	28	4	0	1	21	2	3	0	12.000	81	
May 25 ...	16	51	25	6	0	0	19	8	0	0	12,200	79.5	
Nov. 15....	18	49	25	7	1	0	20	7	3	2	10,200	79.5	
Nov. 22....	..	..	..	..	..	..	..	..	..	..	12,000	....	
Nov. 25....	9	38	38	13	2	0	12	4	2	0	14,600	66	
Nov. 29....	..	..	..	..	..	..	..	..	..	..	14,200	....	
1909													
Feb. 28....	17	43	30	8	2	0	17	7	4	0	13.000	75	
Mar. 9.....	8	43	34	14	4	0	21	14	1	0	13,200	66	
Mar. 21....	Reacted to tuberculin.												
Mar. 23....	11	37	42	8	2	0	9	8	3	0	14,000	69	
Mar. 27....	12	37	30	18	3	0	15	9	4	0	12,000	64.5	
Apr. 3.....	10	38	33	18	1	0	12	5	3	1	13,400	69.5	
Apr. 27....	11	37	32	16	3	0	17	9	4	1	12,800	64	
May 4.....	13	40	35	9	3	0	10	5	1	1	13,000	70.5	
May 18....	9	44	33	13	1	0	15	8	1	1	14,000	69	

Died during the summer.

PATIENT B.—A young woman who has shown decided improvement under the tuberculin treatment. She has returned to work, and except for a bad cold has been well all winter.

Date	1	2	3	4	5	6	L.L.	S.L.	E.	M.	Leuc.	Index
1907												
May 3.....	9	38	36	16	1	0	0	0	0	0	.....	65
May 6.....	8	39	35	17	1	0	0	0	0	0	.. ...	64
May 17..... ...	9	36	42	10	3	0	0	0	0	0	.....	66
May 29.	6	20	37	29	8	0	0	0	0	0	9,000	44
May 31.....	5	27	37	28	3	0	31	23	4	0	7.800	50
June 7.....	8	36	35	19	2	0	0	0	0	0	8,000	61
June 10.....	8	18	32	31	11	0	25	23	1	0	9,000	42
June 24.....	10	27	29	25	9	0	36	8	2	0	10,000	51
	Away for summer.											
Sept. 31.....	2	13	31	41	13	0	31	24	1	..	9,000	46
Oct. 4	4	22	42	27	5	0	30	28	2	0	8,800	47
	Gone back to work.											
Dec. 13.....	Has bad cold.											
	8	34	38	18	2	..	20	18	3	0	10 000	61
	Away at work.											
1908												
March 16.....	5	21	43	26	5	0	36	39	8	0	10,000	47

PATIENT E.—A married woman with two children whose husband had died with tuberculosis some years before. This patient received the tuberculin treatment, but never improved noticeably, and finally died in February, 1908.

Date	1	2	3	4	5	6	L.L.	S.L.	E.	M.	Leuc.	Index	Remarks
1907													
June 14 ..	16	40	24	16	4	0	18	12	3	2	12,000	68	Tuberculin.
June 21...	17	49	23	11	0	0	10	12	4	0	11,600	78.5	
June 24...	23	41	26	8	2	0	9	10	4	1	12,200	77	
Sept. 31...	22	37	29	12	0	0	25	7	2	0	12,000	73.5	
Oct. 4. ...	23	42	23	8	4	0	9	7	2	1	9.000	77.5	
Oct. 11....	26	45	17	11	1	0	14	1	0	2	10,600	79.5	
Oct. 14 ..	21	51	20	7	1	0	18	2	1	1	13,200	82	
Oct. 25 ...	24	41	24	9	2	0	27	8	4	0	10,000	77	
Nov. 1....	26	48	16	10	0	0	34	18	4	0	12,000	82	
Nov. 8....	26	39	22	12	1	0	12	8	5	0	12,600	76	
Nov. 11 ..													
Nov. 15...	17	38	28	15	2	0	16	5	5	1	13,000	69	
Nov. 18...	10	49	26	15	0	0	22	6	8	1	12,000	72	
Nov. 22...	20	50	20	10	0	0	12	4	5	0	15,000	80	
	Ill.												
Dec. 16....	24	49	20	7	0	0	16	5	4	1	18,000	83	
Dec. 20....	25	48	19	8	0	0	15	4	3	1	14,000	82	
1908													
Jan. 10....	26	52	13	0	0	0	6	1	1	0	18 000	84.5	

The study of the many blood pictures made from these cases together with the clinical data showed that all the cases where, through several observations, the blood pieture gave a shifting to the left without an increase in the number of large lymphoeytes and without a decided leucocytosis, the tubereulosis baeilli were either found in the sputum or the patient showed the clinical signs of tubereulosis. However, where there was but a slight shifting to the left with one observation, these cases sometimes developed into something other than tubereulosis. Also a number of eases of poor resolution in pneumonia gave the tubercular blood pietnre except that in these eases the number of large lymphocytes usually remained higher than in tuberculosis and the number of eosinophiles inereased. These observations led to the conelusion that this blood pietnre was not of great value in diagnosis except where a number of observations eould be made. In this ease then, Arneth's neutrophilic blood pieture whieh takes no aecount of the other cells of the blood ean have no diagnostic value. It was hoped that this blood pietnre would prove of great value in detecting ineipient eases where the clinieal signs were not clear, but unfortunately the blood picture is not of much diagnostie valne there. The study of these blood pietures did show, however,

that it is of great value in prognosis as it is a much more delicate and certain indication of the patient's condition than any other clinical sign.

These observations upon tubercular patients suggested a number of experiments in order to understand as far as possible the changes which take place in the blood picture. These experiments were largely carried out at the *Institut für Infectionskrankheiten,* Berlin, Germany. A few of the most interesting are given below.

1. Various fixing and staining experiments.

This was partly suggested by a paper of Pollitzer's which appeared in 1907 and condemned Arneth's work on the ground that the lobes of the nucleus were artifacts due to killing and fixing and especially to Wright's method of differential staining, and also partly suggested in an attempt to find the best method for preparing the blood smears so as to get the clearest nuclear picture for the blood count. Blood smears from three subjects whose neutrophilic indices were 45, 52 and 60 were spread as thinly and as evenly as possible upon slides, which were absolutely clean and as sterile as conditions permitted. These smears were killed in most of the well known cytological methods such as osmic acid, strong Flemming, formalin, corrosive acetic, hot alcohol acetic and various others, also many were dried and then treated with methyl alcohol. One slide from each of the above methods of killing was then stained either with Wright's differential blood stain, Jenner's blood stain, methylene blue and eosin, iron hematoxylin, Delafield's hematoxylin and eosin or with safranin, acid fuchsin and orange G. All the slides gave a more or less clear nuclear picture. Those killed with strong Flemming or osmic acid and stained with iron hematoxylin were the least satisfactory, while those killed with hot alcohol sublimate and stained with iron hematoxylin gave the clearest and best nuclear picture, but of course this method is useless for bedside work. Wright's was the most satisfactory method because it was the simplest and gave a very good nuclear picture as well as differentiated the different types of leucocytes. Jenner's stain was useless in that the nuclear picture was poor. The other methods gave good nuclear pictures, but not better than Wright's. The slides prepared were all counted with a key so that at the time they were counted it was not known from which of the three subjects the smear had been made. All the smears from any one of the three subjects gave practically the same index and the indices for the smears from the three subjects remained the same regardless of how the smear had been killed and stained. These experiments establish the fact that the state the nucleus of the neutrophile assumes in the killed and stained cell is something definite and dependent upon the state of the living cell and is not dependent upon the method of preparation. They also show that Wright's method is the best method of preparing smears for the neutrophilic blood picture. It was found that blood cells will live on an agar medium sometimes for several days and in observing these living cells it was seen that there are certain times when the nucleus shows up as a clear refractive body surrounded by the granules and in preparations made from the blood of normal subjects all the classes found in the stained preparation are to be observed among these living cells. Also if a thin smear is made over an agar plate and this is passed over chloroform vapor, the nucleus stands out as above and this preparation will give the same neutrophilic count that the stained preparation from the same subject gives.

Another experiment, that of stretching the nucleus was tried in order to see whether what appears to be one lobe could be drawn apart into several. Pollitzer claims that what appears to be but one lobe of nucleus is really many pieces of the nuclens lying close together (Fig. 24), and made to seem as one by the stain. Slides were scratched with emory paper and then the drop of blood drawn slowly across these scratches in order if possible to catch and tear the cells in the scratches. Although the cells of these preparations were badly torn and stretched the neutrophilic blood picture remained the same as when smears from the same subject had been prepared in the usual manner. Figures 25 and 26 show the neutrophile badly stretched but the nucleus is also stretched and does not give a greater number of lobes than normally.

2. The normal blood picture in man and in guinea pigs.

Smears were prepared from about thirty different subjects whose condition was, as far as known, normal. These different blood pictures gave indices, which varied slightly from each other and yet varied within a small range, which could be called normal. This blood picture corresponds as far as the neutrophiles are concerned very nearly with that of Arneth, which was taken from a large number of cases.

Smears were obtained from a few subjects at different times of day extending over periods of a week or several weeks and in two cases extending at intervals over a period of two years. The results in these cases, show indices, which vary but not definitely enough to be attributed to any one cause and the amount the index varied was usually so slight as to still come within the normal blood picture, which for man is

Class	I	II	III	IV	V	L.L.	S.L.	E.	B.	W.B.C.
	5	22	42	26	5	22	18	1	0	8,000

Ten guinea pigs were studied, for a period of two weeks. Smears were made from drops of blood taken from the ear every two or four hours during each daytime. The results gave a blood picture comparable to that of man except that the neutrophile usually has a larger number of lobes than in man.

Class	I	II	III	IV	V	VI	L.L.	S.L.	E.	B.	W.B.C.	Index
	5	20	34	30	6	5					10,000	42 : 58

The blood picture as shown by guinea pigs varied so much more for the individual animal than it did for the individual person, that in all experiments with guinea pigs smears were made from the animal each day for a week or ten days before the experiment in order to obtain the normal for each animal.

3. The effect upon the neutrophilic blood picture by inoculation of virulent cultures of tuberculosis bacilli.

Guinea pigs were inoculated subcutaneously with varying amounts of an emulsion of a culture of virulent tuberculosis bacilli. They all gave a blood picture much like the one which follows, except, that those animals, which received a larger quantity or a stronger emulsion of the bacilli, showed the

typical tuberculosis condition more quickly, while those, which received a smaller quantity or a weaker emulsion reached that condition more slowly.

Guinea Pig VI, Inoculated with 3-Cmm. Strong Emulsion of Tuberculosis Bacilli.

	I	II	III	IV	V	VI	VII	VIII	W.B.C.	Index
Before inoculation..	3	21	32	33	6	5	..	..	9,000	40-60
At time of inocultn.	4	19	36	30	6	5	..	..	9,600	41-59
3 hours after.....	2	14	28	34	12	— 10	.	..	10 000	30-70
12 hours after.... ..	2	4	16	34	19	10	10	5	10,200	13-87
24 hours after.....	2	5	18	36	20	11	6	2	15,000	16-84
48 hours after... . ..	3	9	18	38	16	10	6	..	16.400	21-79
4 days after.....	3	12	38	34	8	3	2	..	14,000	34-66
8 days after.....	4	18	38	30	8	2	..	..	13,200	41 59
12 days after....	8	22	39	24	5	2	..	..	13.400	49-51
18 days after.....	16	38	40	6	..	..	..	..	13,200	74 : 26
21 days after.....	23	45	32	..	..	..	..	..	12.000	84 : 16
25 days after.....	24	53	23	..	..	..	..	..	13,000	87 : 13

Killed—Lungs, liver, and spleen full of tubercles.

These blood pictures show that within a few hours after the inoculation there is an increase in the number of neutrophiles with the larger number of lobes to the nucleus, *i. e.*, the blood picture shifts to the right, and then follows an increase in the number of leucocytes. The shifting to the right of the blood picture remained a few days and then gradually returned to normal. After ten days or two weeks, in some cases longer, the number of lobes of the nucleus began to decrease, *i. e.*, the blood picture began to shift to the left while the number of leucocytes remained about the same or increased very much in dying cases. This condition continued until there were present in the blood only those neutrophiles with a nucleus of one, two or three lobes.

4. Blood on agar media with tuberculosis bacilli.

In 1908 it was found that bone-marrow cells, or blood cells will live and divide when kept on an agar medium (agar 0.5 gm., bouillon 20 cc.+Locke's sol. 80 cc.) in a Petri dish at 37° C.

A large drop of fresh flowing human blood was placed on an agar plate; to one side of the drop was placed a very small point of virulent tuberculosis bacilli. The agar plate was then kept at 37° C. and smears were made every five minutes from the side of the drop next to the bacilli as well as from the side away from the bacilli. The blood pictures showed an increase in the number of lobes of the nucleus of the neutrophiles from the side of the drop which touched the bacilli in as short a time as 10 or 15 minutes, while the nucleus of the neutrophiles from the side away from the bacilli remained normal. Leucocytes washed free from the plasma by the same method as is used in the opsonic work give the same results as the blood leucocytes.

5. Neutrophilic blood picture in the opsonic work with tuberculosis bacilli.

Many of the slides studied were obtained through the courtesy of Dr. Park of the Board of Health, New York City, and others were prepared by the observer. A standardized emulsion of dead bacilli was used with washed leucocytes and incubated 15 minutes at 37° C. In all cases the blood picture from these smears showed a decided increase in the number of lobes of the nucleus of the neutrophiles. Neutrophiles with nuclei of 6, 8, 10, 12 and in one case 16 lobes were found (see Figs. 27 and 28). On the other hand sterile washed leucocytes without the addition of the bacilli, incubated 15 minutes did not undergo any change with regard to the neutrophilic blood picture.

An interesting observation in this experiment is that the neutrophiles taken from tubercular subjects show a great difference in their ability to react to the tuberculosis bacilli in this manner, which shows itself by an increase in the number of lobes of the nucleus of the neutrophile. Washed leucocytes from a subject in an advanced stage of tuberculosis do not react at all. The fact that neutrophiles from different cases react in different degrees shows that the serum of the blood is not the only important factor in the greater or less resistance of the individual to bacteria and quite agrees with the argument presented by Vietch, in his paper on a new opsonic method, that it is a surer as well as a simpler method to take the leucocytes from the same individual as the serum is obtained, on the ground that the serum is but one part of the blood, while the whole blood is concerned in the resistance. Although it is at present impossible to say just what this change of the nucleus of the neutrophiles means, the fact that it does change at all, shows that the neutrophile is sensitive to its environment and probably plays an important part in the resistance. It is possible that this may show what Arneth claims, *i. e.*, that the older forms are used up by coming in contact with the bacilli. However, this reaction is in no way one of degenerative fragmentation, as may be seen from Figs. 27 and 28. The nucleus of 8 or 10 lobes is as healthy looking as the one of 3 or 4 lobes.

6. Effect of contamination.

Blood drawn from the end of a finger purposely made dirty and smeared on a slide, which was not clean, gave a blood picture which showed a slight increase in the number of lobes of the nucleus of the neutrophile. Blood was drawn from a sterile finger and placed both in small glass chambers, which were sterile and in others, which were dirty and incubated 10 minutes. That in the sterile chambers gave a normal neutrophilic blood picture while that in the dirty chambers gave a blood picture in which some of the neutrophiles had a nucleus of 8 or 10 lobes (Figs. 29 and 30).

Guinea Pig X developed an open abscess at the point of entrance of the needle, and the subsequent blood pictures instead of resembling those of the tubercular guinea pig showed a decided shifting to the right, due to the infection with a pyogenic bacterium.

7. Effect of inoculation with snake venom.

Guinea pigs or rabbits were inoculated with small quantities of snake venom and smears made from blood from the ear, also from the bone-marrow cells. The blood pictures from these smears showed all the neutrophiles with nuclei of many lobes and often so many lobes that the nuclei had the appearance of a rosette.

The conclusions from these experiments are, first, that the neutrophile is a delicate organism, which reacts quickly and definitely to its environment and that this reaction may in a measure be judged by the condition of the nucleus, *i. e.*, by the

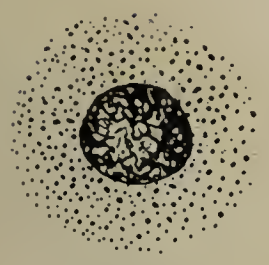


FIG. 1

FIG. 2

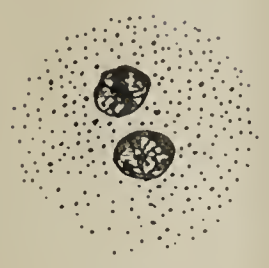


FIG. 3

FIG. 4

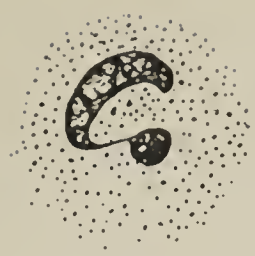


FIG. 5

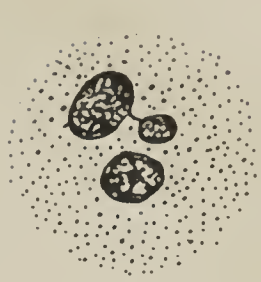


FIG. 6

FIG. 7

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FIG. 21

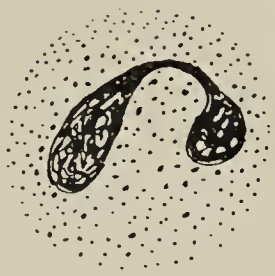

FIG. 22

FIG. 23

FIG. 24

FIG. 25

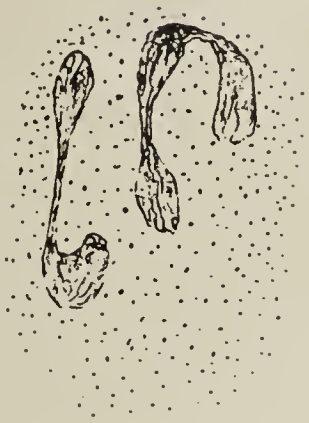

FIG. 26

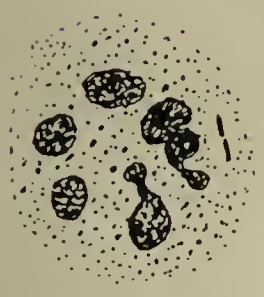

FIG. 27

FIG. 28

FIG. 29

FIG. 30

DESCRIPTION OF FIGURES.

Figs. 1-20. Neutrophiles whose nuclei show the number of pieces according to the classification of Arneth's blood picture.

Fig. 21. Neutrophile with a bent nucleus, which is counted as one lobe.

Figs. 22 and 23. Neutrophiles with a bent nucleus, which is counted as two lobes.

Fig. 24. Drawing taken from Pollitzer's paper to show many pieces of the nucleus.

Figs. 25 and 26. Torn neutrophiles with stretched nuclei.

Figs. 27 and 28. Neutrophiles with many lobed nuclei ingesting tubercle bacilli.

Figs. 29 and 30. Neutrophiles with many lobed nuclei due to contamination.

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number of lobes of the nucleus. Second, that when the nuclei of the neutrophiles have a larger number of lobes than normal, it probably indicates some immediate reaction of the neutrophiles to a change in their environment, such as snake toxin or the presence of some bacteria. Third, that when the neutrophiles have nuclei with fewer lobes than normal, they are probably reacting slowly to some change in their environment, so that the neutrophiles with the larger number of lobes of the nucleus are used up and only those with the fewer lobes are left in the circulating blood or else that the neutrophiles fail to react in such a way as to cause a change in the nuclei and so remain in almost the same condition as that in which they entered the blood. Fourth, that the neutrophilic blood picture index, shows the condition of the nuclei of the neutrophiles and since the condition of the nucleus is probably an indication of the condition of the neutrophiles of the blood, we can judge to some degree by the means of the neutrophilic index of the condition of the patient.

In the spring of 1910, Dr. Miller turned over to Mr. C. J. Diolet, an expert statistician, all the blood pictures as well as all the clinical evidence upon the cases observed at the Bellevue Hospital and from this data Mr. Diolet formed a number of statistics and charts, which will appear in a paper in collaboration with Dr. Miller. A few of the most interesting of these are briefly quoted below.

1. The number of leucocytes in incipient tuberculosis is between 9874 and 10,209; while this is slightly higher than most observers have found, it is not markedly different. There is a distinct increase in the number of leucocytes with the progress of the disease. Moribund cases show a marked leucocytosis of 26,300. The number of leucocytes in tuberculosis is of itself of much prognostic value since in these observations their number corresponds with the subsequent (2 years) history.

2. The percentage of neutrophiles varies from 64.4 in non-tubercular cases to 78.5 in dying tuberculosis cases. This increase of the neutrophiles in the more unfavorable cases is very marked and indicates an unfavorable prognosis.

3. The large lymphocytes according to the statistics show no apparent relationship with the progress of the disease.

4. The small lymphocytes on the other hand did show a very close connection with the course of the disease and this connection might of itself be used as a means of prognosis. In non-tubercular cases and in incipient cases, those cases with good prognosis and those cases whose subsequent history showed improvement gave between 9 and 11 per cent of small lymphocytes. The more advanced cases show between 4.1 and 6.2 per cent, while the moderately advanced cases and those with doubtful prognosis stand between and have between 7.5 and 7.9 per cent.

5. The eosinophiles decrease with the progress of the disease until in dying cases they are entirely absent.

6. The basophiles give no definite results.

7. The neutrophilic blood picture was represented only by the index. The average index for non-tubercular cases is 54-46, the far-advanced cases 75.25 and all stages in between have a corresponding shift to the left in the index. The changes noted for the neutrophilic blood picture were more constant than any other change in the blood and much more so than any of the usual clinical signs and symptoms. In diagnosis the usefulness of the neutrophilic blood picture is not great when taken by itself as other conditions may give a slight shifting to the left, but when considered in connection with the other blood cells and when more than one observation is made, it may be of diagnostic value. In prognosis, however, both at the time of examination and during the course of the disease, the degree of shifting to the left is an exceedingly sensitive indication of the resisting power of the individual and of the progress of the disease.

Cases with slight lesion but unfavorable blood picture almost invariably do badly, but, on the contrary, those with extensive lesions and fairly good blood picture show a marked tendency to resist the disease. Moreover, it has been found during the clinical observation of a case that its real progress, in one direction or the other, can usually be more accurately anticipated by the change in the blood picture than by any other clinical means. Even clinically apparent cures are insecure unless the blood picture has come to approach the normal.

W.B.C.	Neutrophiles	L.L.	S.L.	E.	B.	Index
1. Non-tubercular cases.						
10,209	64.4	17.5	18.8	5.8	.53	54-46
2. Incipient tuberculosis.						
9,874	72.4	14.4	9	3.7	.52	64 36
3. Advanced tuberculosis.						
10,200	74	15.2	7.9	2.4	.52	67-33
4. Far advanced tuberculosis.						
13,208	77.9	13.9	6.2	1.5	.44	75-25
Cases with good prognosis.						
9,398	71.8	14.8	9.1	3.7	.53	60-40
Cases with poor prognosis.						
12,488	77.1	13.4	7.5	1.6	.35	72-28
Cases which showed subsequent improvement.						
9,323	71.6	14.9	9.9	3.0	.56	60-40
Cases which subsequently did badly.						
13,897	77.3	14.5	5.9	1.86	.43	75-26

Through the kindness of Dr. George Lockwood and Dr. William Draper, of the Bellevue Hospital, a number of observations were made in connection with Dr. J. Alexander Miller upon cases of pneumonia and later through the kindness of Dr. Lewellys F. Barker, the same work was continued at the Johns Hopkins Hospital. So far the results have not proved definite from the statistic side, but in the individual case it is of prognostic value; especially is it of value in determining whether a case of delayed resolution is tubercular or not. Some cases showed a marked shifting to the right and the lobulation of the nucleus reached 7 or 8 pieces. Such cases showed purulent infection at the post mortem examination. The eosinophiles remain normal during acute stages, but increase afterwards, especially in cases of delayed resolution.

Most cases showed a moderate shifting to the left of the neutrophilic blood picture, giving an index anywhere from 60-40 to 80-20, which index tends to return to normal upon defervescence with good resolution.

In six cases of delayed resolution the index 64-36 continued

high, while the number of leucocytes decreased to normal or below normal, and the number of large lymphocytes decreased. These cases gave a typical tubercular blood picture and later the bacilli were found in the sputum.

In the three cases of appendicitis, the blood picture showed a decided shifting to the right, and neutrophiles with nuclei of 6, 7 and 8 lobes were present. Upon operation these cases showed a purulent condition of the appendix, while in one case where the blood picture was practically normal the operation showed no infection of the appendix.

Several cases of abscess showed the shifting to the right in the early stages. The following are a few typical blood pictures.

	Class I	II	III	IV	V	VI	VII	L.L.	S.L.	E.	B.	W.B.C.	Index
Normal.....	5	22	42	26	5	..	..	20	10	1	0	8,000	48-52
Tuberculosis..	14	40	36	10	..	..	..	18	5	1	0	12,000	72-28
Pneumonia...	20	40	30	10	..	..	..	32	8	1	0	18,000	75-25
Pus case	4	14	18	32	21	9	2	12	6	1	1	24,000	27-73

The conclusions from these observations may be briefly stated as follows:

The neutrophile is an organism, which reacts quickly and definitely to its environment and the condition of the nucleus as shown by the number of lobes, may be taken as an indication of the condition of the neutrophile. Under normal conditions the nucleus does not show more than five lobes, but the presence of certain abnormal conditions may cause it to show as high as 8 or 10 lobes, while certain other conditions, such as tuberculosis, may prevent it from having more than 1, 2 or 3 lobes. These changes of the nucleus together with the other blood cells and the number of white blood cells form a picture, which can be used to determine the condition of the patient.

This neutrophilic blood picture together with the differential blood count is of great value in prognosis in tuberculosis, but not of much value in diagnosis. It is of value in determining the presence of pyogenic bacteria in pneumonia or an abscess and may be of value in detecting a purulent condition of the appendix. In connection with the number of white blood cells and the number of lymphocytes it is of value in distinguishing between a case of poor resolution in pneumonia and tuberculosis.

It is of especial value in the prognosis of any disease where it is of use to determine the metabolic activity of the patient or the resistance to disease as any condition of lowered vitality is quickly detected by this blood picture.

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NOTES ON NEW BOOKS.

A Text-book of Gynecological Surgery. By Comyns Berkeley, M. D., M. R. C. S. (Eng.), etc., and Victor Bonney, M. D., F. R. C. S. (Eng.), etc. (*New York: Funk & Wagnalls Co., 1911.*)

This work describes briefly but clearly the technique of the various gynecological operations as practiced by one of the leading schools of English gynecologists. It discusses also operative indications and dangers, as well as ante-operative preparation and post-operative treatment and complications. There are numerous black-and-white schematic illustrations and a considerable number of colored plates, all of which are of mediocre artistic merit, but nevertheless are quite helpful in elucidating that text. The authors have succeeded admirably in presenting a very complete treatise in a condensed and readable form, which will doubtless be gratefully received by the American profession.

E. H. R.

Dyspepsia: Its Varieties and Treatment. By W. Soltau Fenwick, M. D. (London). Illustrated. Price, $3.00 net. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

This work treats of disorders which are certainly frequent enough to justify a special discussion of their features. One searches at once for a definition of the term dyspepsia, but the author, probably very wisely, does not give one in set words. Perhaps he considered that the text sufficiently described what he included under the term. The author points out certain things which are essential to keep in mind if one is to have any clear ideas of this subject. One is that a disorder of digestion is rarely due to primary disease of the stomach. This is one point often entirely disregarded in practice and when it is more fully recognized there will be a falling off in the use of many drugs given for gastric disorders. In this connection, however, the author does not seem to attach enough importance to gastric derangement secondary to general nervous disturbance. He gives the principal place to primary disease of the liver, pancreas or bowel. These play a part but it is doubtful if it is the main one. Then he takes a fling at the terminology employed for gastric disorders; with this we are in hearty agreement. He seems to have written a volume on gastric disorder without coining any new terms for which commendation is due and it is to be hoped the example will be followed by those who come after. Of intestinal indigestion he says that it "almost defies chemical analysis," which is a comforting statement when we are in despair over our inability to properly classify examples of it.

Of this work as a whole it can be said that the discussion is well done, the descriptions accurate and the treatment sensible. However, there are some statements which should be qualified. Thus it is not safe to make a diagnosis dogmatically in

the presence or absence of one particular symptom. For example, to state that in hyperacidity there is no vomiting is hardly correct. The use of the term gastric neurasthenia is not to be commended. Why not as well speak of gastric psychasthenia or gastric hysteria? In the discussion of the so-called gastric neurasthenia, the author seems to put the cart before the horse. Thus the text suggests that the often accompanying mucous colitis is in consequence of the gastric disorder, whereas both are usually results of a common cause.

There is an excellent section on dyspepsia which occurs secondary to other diseases with particular reference to the disturbances in tuberculosis. The discussion of the digestive disorders of infancy and old age is useful and worthy of special note, especially the latter section. The care of the health of the aged is worthy of more attention than it usually receives.

Altogether this work is to be commended as an excellent guide in the management of the various forms of dyspepsia. The treatment advised is usually sound but there are some points which might be given more emphasis. For example the need of attention to the teeth hardly seems to have received sufficient mention. Often a dentist is needed more than a physician. Again the question of proper chewing of the food would seem worthy of more notice than it receives. But these suggestions must not be regarded as serious criticisms and Dr. Fenwick is to be congratulated on the excellent volume which he has written on a difficult subject.

The Practice of Medicine: A Guide to the Nature, Discrimination and Management of Disease. By A. O. KELLY, A. M., M. D., Assistant Professor of Medicine in the University of Pennsylvania and Assistant Physician to the University Hospital, Philadelphia. Illustrated. (*Philadelphia and New York: Lea & Febiger. 1910.*)

This excellent text-book is a monument to the industry and ability of its author, who was so recently cut off at the height of an active and successful medical career. Although a comparatively young man, few clinicians were better equipped to write a text-book on medicine. Dr. Kelly was a keen clinical observer and his bedside training was supported by an extensive pathological experience in the autopsy room. His thorough familiarity with medical literature has enabled him to incorporate in this volume of 945 pages, practically all the important recent contributions to our knowledge of medical affections. Although the author states that the volume is intended especially for medical students and the junior practitioners of medicine, nevertheless the teacher of medicine can turn to its pages with a certainty that he will find the most modern views concerning the etiology, symptomatology, pathology and management of the various medical diseases dealt with.

The subject matter is treated under twelve sections. These are arranged in the following order: Infectious Diseases; Intoxications; Disorders of Metabolism; Diseases of the Ductless Glands and of Internal Secretions; Diseases of the Blood and Hemopoietic System; Diseases of the Circulatory System; Diseases of the Respiratory System; Diseases of the Digestive System; Diseases of the Urinary System; Diseases of the Nervous System; Diseases of the Muscles; Diseases of the Bones and Joints.

The author has made an interesting subdivision of the infectious diseases. The first takes up the bacterial infections, which include the various diseases which are now known to be due to a specific organism. Then come the non-bacterial fungus infections including such conditions as actinomycosis and pulmonary aspergillosis. The subdivision of zoöparasitic infections embrace the protozoan infections such as amœbiasis, syphilis and malaria and the metazoan infections under which are described the intestinal, visceral and cutaneous parasitic diseases.

With our advancing knowledge, one of the great difficulties of an author must be to keep a text-book on medicine within reasonable bounds as to size. This the writer has been able to do. While some diseases are of necessity treated briefly, yet it is difficult to find a single affection that has escaped the writer's attention. The student and practitioner will find this volume a most useful addition to his medical equipment.

The Surgery and Pathology of the Thyroid and Parathyroid Glands. By ALBERT J. OCHSNER, A. M., M. D., LL. D., and RALPH L. THOMPSON, A. M., M. D. (*St. Louis: C. V. Mosby Company, 1910.*)

In the preface the authors state that they have planned to bring to the practitioner of medicine and surgery the results of the study of the work of those who have given much time to the development of this special field.

The work of 334 pages is divided into two parts, the first by Dr. Ochsner on the thyroid, the second by Dr. Thompson on the parathyroid glandules. Dr. Ochsner's experience in thyroid surgery has been so large and varied that anything written by him demands the attention of both surgeons and internists. In the first part he discusses the surgical considerations of the thyroid gland, its pathology and the diagnosis and treatment of its diseases, both medical and surgical. Considerable space is devoted to the various operations on the gland, and the technique of these operations is well described and profusely illustrated. Chapters follow on the prognosis in exophthalmic goitre and heredity in goitre.

The second part, by Dr. Thompson, deals with the anatomy, histology and tumors of the parathyroid glandules, and their importance in operations upon the thyroid gland. Our knowledge of these interesting organs has been brought together by the author in a most concise manner.

The book is well written and will be a great help to those who wish to find a resumé of our knowledge of these organs in a comparatively small space.

Atlas of Microscopic Diagnosis in Gynecology. With Preface and Explanatory Text. By DR. RUDOLF JOLLY, Priv. Doc. Only Authorized English Translation. By DR. P. W. SHEDD. Illustrated. Price, $5. (*New York: Rebman Company, 1911.*)

Familiarity with the normal and pathologic histology of the female organs of generation is of fundamental importance to the gynecologist. Thus, for example, uterine hemorrhage is an exceedingly common symptom, quite often met with independent of any demonstrable gross lesion. In such cases the aid of the microscope must be sought, and forthwith one is confronted by the fact that there is quite a list of endometrial changes capable of producing this symptom, some of which may very closely simulate each other in histological appearance. Unfortunately, the most important diagnosis to be made, namely, that of malignancy, is thus rendered the most difficult. The vital importance and moral responsibility involved in such a determination is, of course, obvious. It seems strange, therefore, that nearly all American works on gynecology, although excellent in other respects, are so conspicuously deficient in microscopic diagnosis. This English translation of Dr. Rudolph Jolly's excellent atlas will on this account prove most acceptable. The bulk of the work, happily, is concerned with physiological and pathological changes in the endometrium, which is of paramount practical importance. The plates are accurate reproductions of microscopic preparations, and are of an unusually high order of excellence. The descriptions, although a bit stilted in phraseology, are judiciously short and comprehensive. Dr. Shedd is due the gratitude of the entire profession for his labor, but more especially of those whose reading is of necessity confined to the English language. The book should meet with ready acceptance.

E. H. R.

Interne Klinik der Bosartigen Neubildungen der Bauchorgane. Von Priv.-Doz. Dr. Rudolf Schmidt. Price, Mk. 14. (*Berlin und Wien: Urban & Schwarzenberg; New York: Rebman Company. 1911.*)

This book is divided into three parts: A, General; B, Special; and C, Case Histories. Parts A and B together cover 175 pages, and Part C about 150. The author lays especial stress on his work on early and differential diagnosis, and also on subjective phenomena, "which are so often precursors of objective findings." In Part B he describes cancer of the stomach (*Magenkrebs*), carcinoma of the large intestine (*Carcinome des Dickdarmes*), primary and secondary cancer of the liver, carcinoma of the gall-bladder, of the pancreas, malignant new growths of the kidney, and atypical malignant tumors of the abdomen. Students who can read German will find this work a useful guide in their study of these varied tumors.

Gynecological Diagnosis. By Walter L. Burrage, A. M., M. D., etc. Illustrated. Price, $6.00. (*New York and London: D. Appleton & Co., 1910.*)

In view of the superficiality, incompleteness and practical worthlessness of many present-day medical works, it is distinctly refreshing to meet with this excellent treatise of Dr. Burrage's. Not only is the book conspicuous for its thoroughness, logical arrangement, clearness and literary excellence, but the author has displayed wise selective judgment in the choice of subject-matter. Every chapter bears the unmistakable earmarks of ripe knowledge and careful preparation. There has been modestly and gracefully incorporated, too, just a satisfying amount of the author's own views and statistics, based upon a large and varied clinical experience, to stamp the book with individuality. While, on the other hand, the numerous references to both the older as well as the very recent literature, at the same time that it adds a further attractive and valuable feature to the work, indicates clearly also the author's breadth of mind and healthy regard for the work of others.

Chapters on diagnosis of vesical, ureteral and rectal disorders, the gynecological affections of infancy and childhood, and on the menopause and old age are very properly included in the work, and are sufficiently full to be both instructive and suggestive.

The chapters on diagnosis of uterine pregnancy, abortion, hydatidiform mole, and on diseases of the breast emphasize not only the close relationship existing between gynecology and obstetrics, on the one hand, and general surgery, on the other, but also the need of constant vigilance on the part of the specialist lest he become narrow and distorted in medical perspective.

The illustrations are well chosen, clear and helpful, and the publishers' work has been well done. There is appended also an excellent index.

Altogether the work speaks most creditably for the scholarship and scientific attainment of its distinguished author, and can be heartily recommended to students, practitioners and specialists alike. It is a distinct addition to gynecological literature and deserves the unstinted support of the profession.

E. H. R.

A Text-book of Mental Diseases. By Eugenio Tanzi, Professor of Psychiatry in the Royal Institute of Higher Studies of Florence. Authorized translation from the Italian by W. Ford Robertson, M. D., C. M., and T. C. Mackenzie, M. D., F. R. C. P. (Edin.) Price, $7.00. (*New York: Rebman Company.*)

Professor Tanzi has been so long known as a leader among the Italian psychiatrists and as one of the editors of the *Rivista di Patologia nervosa e mentale* that this translation of his textbook, representing as it does a summary of his views on the subject, will be welcomed by all those interested in psychiatry as giving a more convenient means of reference than the original work. Certain changes have been made in the translation which make it more suitable for English readers, these being the omission of several descriptions of cases, the substitution of English specimens of handwriting, and the omission of the section dealing exclusively with the administration of Italian asylums.

The book is divided into twenty-six chapters, the first entitled The Seat of the Psychical Processes, dealing chiefly with anatomical data as shown by anatomy, pathology, and embryology, which gives us positive evidence of the existence of psychical centres but which Tanzi qualifies by the statement that "The law that the functional processes are always pluricellular also holds, however, for these centres, as does also the law that every cell has the power of resisting or yielding to stimuli, and of reacting in various though similar ways. Further, the activity of a single cell never corresponds to an imaginable figure, whether it be of the most elementary or of the most vaguely symbolical nature, unless it is compounded with that of very many other cells, perhaps thousands, scattered here and there in the brain. For this reason the precise contents of the psychical treasure-house, as also the degree of intellectual activity, will always be an enigma to the anatomist. Only the generic type of the intelligence, the enumeration of the functions that belong to the various cortical centres, and the feebleness or the extraordinary development of a psychical function, are problems capable of solution by anatomy, and of being made the subject of future corollaries through the clinical study of mental diseases." By the study of the brains of exceptionally gifted persons, such as orators, musicians, etc., and of the brains of idiots and partial dements we may discern the outlines of a vast scheme of psycho-pathological anatomy, and psychiatry will cross "the narrow strait which separates it from the other departments of clinical science."

In the second chapter on The Causes of Mental Diseases, Tanzi avoids any prolonged or statistical discussion and comes to the conclusion that, "among the causes of insanity, the external act more widely than the internal; and among the external causes, somatic disorders and social inequalities are more to be feared than intellectual overstrain, which has no harmful effect if not accompanied by hygienic errors and depressing emotions, and, therefore, also by trophic disturbances of the entire organism." A statement which we believe will not be unqualifiedly endorsed by observers in this country.

The next four chapters deal with Sensibility, Ideation, Memory, and The Sentiments. Chapter VIII with Movements and other External Reactions. In Chapter IX upon the Classification of Mental Diseases Tanzi discusses those of Morselli and Kraepelin, and gives one of his own somewhat similar to the latter's but more simple.

The following chapters deal with Pellagra, Alcoholism, Amentia, Thyroid Psychoses, Progressive Paralysis, Infantile Cerebropathies (acquired idiocy), Cerebropathies of Adults, Affective Psychoses, Neurasthenia, Hysteria, Epilepsy, Dementia Præcox, Sexual Perversions, Constitutional Immorality, Paranoia, and Imbecility. Under Amentia are included the exhaustive and infective psychoses, thus making of it a fairly large group. Mania Melancholia and the periodic psychoses are included under the Affective Psychoses. The various obsessions are grouped under Neurasthenia. The chapters on Sexual Perversions and Constitutional Immorality contain many wise reflections which could be read with profit by legislators, magistrates, and all concerned with the administration of laws as well as by the medical profession. Concluding the latter chapter Tanzi says: "If alienists would be firm and unanimous in declaring that congenital immorality is an anomaly, and not a disease, legis-

lators and magistrates would also be more precise and unanimous in assigning to the immoral by nature a treatment that would reassure society, and still be in accord with justice and prudence."

The final chapter on Asylums opens with an interesting account of the development of the modern hospital for the insane and contains much wise criticism and suggestion.

On the whole the book is a valuable addition to psychiatric literature and we should be grateful to the translators for performing their task so excellently. W. R. D.

Die akute Leukämie. Von DR. ALBERT HERZ. Price, Mk. 4.50. (*Leipzig und Wien: Franz Deuticke, 1911.*)

This is a monograph of over 160 pages, based on the personal observation of eight cases, with five autopsies, of acute leukemia. The author worked in Kovác's clinic and Weichselbaum's pathological institute in Vienna, and in conjunction with the special study of his cases, has gone through all the literature bearing on the subject, so that his work is very complete. An excellent bibliography, arranged alphabetically, is to be found at the end of his paper. There are no illustrations. The rare opportunity that Herz has had to follow so many cases to their end makes his monograph of importance to all hæmatologists.

Meningitis, Sinus Thombosis, and Abscess of the Brain. By JOHN WYLLIE. M. D. Price, $3. (*New York: Paul B. Hoeber, 1911.*)

This book is the outcome, so it appears, of reading rather than of personal experience, and so lacks exactness and authority. After looking through certain portions of the symptomatology one is confused by the absence of any clear cut figure of the disease presented. Had the author studied other literature beside the current English magazines he would have written a more valuable work. In his bibliography there are but very few references to foreign sources.

Éliments d' Anatomie Pathologique. Par le DR. L. BÉRIEL. (*Paris: G. Steinheil, 1910.*)

The real workers in pathology who are interested in knowing the modern French point of view on the elements of this study will be glad to have this work. It is mainly intended for students preparing for their examination in this branch of medicine in France and so is intensely practical, all theory and controversy being rigidly omitted. It is illustrated, but for the most part the drawings are not so good as we are accustomed to in our American text-books. It is a concise work of about 550 pages, with the defects inherent to its presentation and purpose—that of serving as a book with which to pass an examination. Written with this end in view, however, it is excellent, and far better than most of its kind.

The Diseases of Infants and Children. By EDMUND CAUTLEY, M. D. (Cantab.), F. R. C. P. (Lond.), Senior Physician to the Belgrave Hospital for Children, etc. Price, $7. (*New York: Paul B. Hoeber, 1910*).

It is difficult for general text-books to keep apace with the additions which are constantly being made to the knowledge of diseases of children. The writer of the treatise before us has succeeded in a large measure in collecting into one volume a discussion of the various ailments to which children are heirs. While the announced object to "describe the conditions in such detail as to render further reference to other works unnecessary, except in the case of unusually rare diseases, has not been fully realized," the volume is of interest for the inclusion of an account of many rare conditions generally omitted in text-books. The book is, in fact, a short system in pediatrics, and will be found particularly valuable as a book of reference.

The impression is given in reading the pages of a carefully prepared summary of the literature but little influenced by the results of the writer's large clinical experience.

Naturally some errors have crept in, as, for example, where on page 49 the globules of cow's milk are said to be 10-15 times as large as those of human milk.

The condemnation, page 51, of laboratory methods in milk modification for the reason that "some babies do badly because of a too low percentage of protein or of fat" is hardly fair to a system which seeks to carry out strictly the physician's orders.

In the discussion of the diarrhœal diseases the reference to the various bacteria, which may play a part in many cases, is inadequate, and the statement that ileo-colitis can only be differentiated from infective diarrhœa by the anatomical changes after death, page 289, is misleading, as the pressure of blood and pus in the injecta indicates in most instances an inflamed or ulcerated bowel wall.

A comparatively large portion of the work is devoted to the consideration of the malformations and congenital defects, and rarer pathological conditions, particularly of the nervous system.

The final section contains a brief but satisfactory reference to the more important affections of the eye, ear and skin.

The treatise as a whole places a valuable text-book in the hands of the advanced student and physician. The publisher's part is well done. One wishes, however, that the size and weight of the volume had been lessened by thinner and lighter paper.

J. H. M. K., JR.

1000 Surgical Suggestions: Practical Brevities in Diagnosis and Treatment. By WALTER M. BRICKNER, B. S., M. D., etc. Fourth American Edition. Price, $1. (*New York: Surgery Publishing Company, 1911.*)

The popularity of this work is an unfortunate index of the mental attitude of a large number of surgeons, who expect to learn surgery by simple rules rather than by a thorough grounding in the science. If such books find readers and publishers, this one can be recommended as giving what is apparently wanted by many.

Report from the Pathological Department, Central Indiana Hospital for Insane. Vol. II, 1906-07, 1907-08; Vol. III, 1908-1909. (*Indianapolis: Wm. B. Burford, Contractor for State Printing and Binding.*)

One of the best evidences of the advance in medical education and improvement in hospitals of all sorts is the recognized value of the pathologist to all institutions treating the sick; and it is a noteworthy fact that the insane hospitals throughout the country are now appointing pathologists on their staffs, and publishing annual reports from the pathological and clinico-pathological departments. Every endeavor of this nature is worthy of commendation and imitation; and the publication of the above reports will help all the physicians in Indiana and elsewhere who are awake and eager to seize the opportunities for instruction that are afforded them. They may not have many readers, but capable young physicians will be more attracted to look for situations in the State hospitals if they know their work is to be supported by pathological investigations; and the present residents will be kept up to a higher level of work. It is only the dullest interne—and he should not have the position—who is not interested when he is able to secure an autopsy on a patient who has been under his observation. In addition to this the accumulating value of pathological reports on autopsies among the insane is very great,

even when the findings may be to use the common but very poor expression "negative." These two volumes contain much of interest to alienists, and physicians in hospitals for the insane, both on the clinical and pathological aspects of the work in the Central Indiana Hospital, and we are glad to note that the third volume is twice as large as the second, showing how well the staff has made use of its material. We hope that Dr. Edenharter, the superintendent, will be able to continue to secure the needed aid from the State legislature to pursue the work already so well begun.

Disease in Bone and its Detection by the X-Rays. By EDWARD W. H. SHENTON, M. R. C. S., etc., with Illustrations. Price, $1.60. (*London: Macmillan & Co., Ltd., 1911.*)

This is a useful little monograph, with some beautiful X-ray photographs to illustrate the text. The author has not attempted to write a text-book in any sense of the word, but only to give a few points on the appearance and differential diagnosis, as seen by means of the X-rays, of the following conditions: Inflamation in Bone, Tubercular Disease, Osteo-Arthritis, Growth in Bone, and Osteo-Malacia. For students beginning to work with the X-rays this brief manual should prove distinctly helpful.

A Manual of Practical Inorganic Chemistry Including Preparations and Qualitative and Quantitative Analysis with the Rudiments of Gas Analysis Specially Adapted to Cover Preliminary and Intermediate University Courses and the First Three Stages of the Syllabus of the Board of Education. By A. M. KELLAS, B. Sc. (London), Ph. D. (Heidelberg). Lecturer on Chemistry at the Middlesex Hospital Medical School, Formerly Examiner in Chemistry to the Conjoint Board of the Royal Colleges of Physicians and Surgeons. (*London: Henry Frowde, Oxford University Press, 1910.*)

Introduction to Practical Organic Chemistry Including Qualitative and Quantitative Analysis and Preparations with a Special Appendix on the London University Syllabus, and Schemes of Analysis for Stages 1 and 2 of the Board of Education Syllabus. By the same author and from the same publisher. *Oxford Medical Publications.*

As the title and contents show, these volumes, like many of the English text-books, are chiefly designed to prepare students for certain examinations. They are a mixture of specialized text-book and specialized laboratory manual, differing in arrangement from books in use in other countries. The books are well written and the student preparing himself for the specified examinations by their help should acquire much knowledge of the subjects. E. R.

New Series, No. 41. Scientific memoirs by Officers of the Medical and Sanitary Departments of the Government of India. *Quinine and Its Salts: Their Solubility and Absorbability.* By CAPTAIN A. C. MACGILCHRIST, M. D., I. M. S., etc. Price, 10d. (*Calcutta: Superintendent Government Printing, India, 1911.*)

This is not simply a chemical study of quinine and some of its salts, but a report rather on their physiological aspects, and deals with their proper administration in cases of malarial fever and amebic dysentery. The results found by Dr. MacGilchrist are, in large part, drawn from experiments on guinea pigs, but this does not vitiate their importance. As the correct dosage of quinine for patients suffering severely from malaria is always somewhat problematical, this contribution is helpful in explaining why quinine and its salts do not always act as we should like them to do.

New Series. No. 42. Part I. *The Cultivation of the Bacillus of Leprosy and the Treatment of Cases by Means of a Vaccine Prepared from the Cultivations.* By MAJOR C. R. ROST, I. M. S. Part II. *The Cultivation of the Leprosy Bacillus.* By CAPTAIN T. S. B. WILLIAMS, M. B., I. M. S. Price, 9d. (*1911.*)

The cheapness of these important publications is one of their striking features, and makes it possible for all students to own such of them as they desire. The reports are usually short and well condensed, so that readers are not obliged to wade through pages of matter that, as so often happens, had better have been omitted. Here we have a distinct brief statement of the findings of Major Rost and Captain Williams, and their studies will be read with interest by the many bacteriologists who are at present very busy in working out the various problems in relation to leprosy.

The Experimental Chemotherapy of Spirilloses. By PAUL EHRLICH and S. HATA. Translated by A. NEWBOLD and Revised by ROBERT W. FELKIN, M. D., etc. Illustrated. (*New York: Rebman Company, 1911.*)

This work, a small volume of 160 pages, comprises several sections. That by Hata, "Experimental Basis of the Chemotherapeutics of Spirilla," is a presentation of the results of a masterly piece of work which from the standpoint of description of method employed, for exactness, clearness and conciseness of expression, and for the clear cut nature of the proof brought forward, can well be held up as a standard to be attained by other writers in the field of chemotherapeutics.

The effects of various dye substances and of numerous arsenicals on experimental relapsing fever in mice and spirillosis in fowls is considered, as well as the treatment of syphilitic keratitis and syphilis of the scrotum in rabbits.

Interesting reports on the action of salvarsan on the *spirochæta pertenuis* in the animal body by Henry J. Nichols, (New York), on the chemotherapy of relapsing fever by Iversen (St. Petersburg), and on cases of relapsing fever treated in the Cairo Infectious Hospital by Dr. Bitter and Dr. Dryer (Cairo), are valuable and interesting additions.

Ehrlich in the "Concluding Remarks" deals in a charming manner with the development and progress of the work which he has been directing for years. He also considers the chemistry of dioxydiamido-arsenobenzol, the chemotherapy of trypanosome diseases, methods and technique in the practical testing of drugs, results obtained in chemotherapy and the outlook for future progress.

This book can be heartily recommended to laboratory workers interested in experimental therapeutics and to all students of medicine. L. G. R.

Common Disorders and Diseases of Childhood. By GEORGE FREDERICK STILL, Professor of Diseases of Children, King's College, London, etc. Second Impression. (*London: H. Frowde, Oxford University Press, 1910.*)

This useful work is not intended to be an exhaustive treatise of all the morbid conditions occurring in childhood, but is rather a terse and interesting account of the more usual ailments which have come under the writer's notice in a remarkably large and varied clinical experience. In a measure the book makes available to a larger number of students and physicians than could afford in person the bright and sensible clinical teaching for which the writer is so well known. Any one reading the pages must wish to be able to come under the personal instruction of so wide-awake and interesting a diagnostician and teacher.

With this understanding of the nature of the book and the method of its preparation it is invidious perhaps to criticise or to suggest that references to the work of others, particularly to investigations outside of England, are rarely given.

The first six chapters are largely devoted to a discussion of infant feeding. The importance of breast nursing is, of course, emphasized, and the resources that are at hand to render a given mother's milk more digestible for her child are carefully enumerated.

The methods of modifying cow's milk for the infant are eminently practical, although they might be considered old fashioned and inaccurate by more radical advocates of "percentage feeding."

One misses any allusion to the caloric needs per given weight of the infant, and the danger from carbohydrate and fat injury receiving at present so much attention abroad almost escapes comment.

The writer warmly advocates the boiling or better pasteurizing of milk for infants during the hot season. This view predominates in America.

The tartrated whey made from precipitating the curd with a minimal amount of tartaric acid, is cheap and has been found serviceable in many cases. It deserves wider use in this country. The use of condensed milk and other patent foods for long periods is properly condemned on the basis of long clinical experience.

The chapters on rickets and scurvy are richly suggestive, although the theory that the use of some cereal may be the chief cause of rickets is hardly tenable, and the relation of impure air to rickets is underestimated.

In the discussion of scurvy the value of the classic orange juice, which certainly is curative, receives scant mention.

The chapter on colic, including the diagnosis and treatment of its various forms, will prove helpful to many readers.

The relation of certain obscure ailments in older children to dental caries is given the prominence it deserves.

In the perplexing group of diarrhœal disorders the writer is careful not to make any fine distinctions. The significance of blood and pus in the dejecta, indicating usually an ulcerated condition of the bowel, is not sufficiently emphasized, and the statement that there are very few cases of infantile diarrhœa in which the use of opium is not indicated might be misleading. Certainly in many cases it is contraindicated.

The discussion of the rheumatic affection of children, a condition perhaps more prevalent in England than elsewhere, is particularly clear and helpful. Attention is called to the importance of recognizing as rheumatic many vague muscular pains, of looking carefully and at the right places for the fibroid nodules as well as to the frequent affection of the heart.

The various nervous and mental abnormalities of children receive rather extended consideration in the closing chapters. One would like perhaps to find a somewhat fuller description of the fundamental pathological findings in these and other conditions. This is, however, not the writer's intention. It is rather to confide to the reader the kind of diseases which for many years have been coming under the care of a skillful observer, and to outline what therapeutic measures have proved in his hands most effective in their treatment. In accomplishing this endeavor an exceedingly interesting and valuable treatise, if not a profound one, on the common disorders of childhood has been placed at the disposal of the profession. J. H. M. K., JR.

BOOKS RECEIVED.

Personal Hygiene and Physical Training for Women. By Anna M. Galbraith, M. D. Illustrated. 1911. 8vo. 371 pages. W. B. Saunders Company, Philadelphia and London.

Vaginal Celiotomy. By S. Wyllis Bandler, M. D., with 148 original illustrations. 1911. 8vo. 450 pages. W. B. Saunders Company, Philadelphia and London.

State Board Questions and Answers. By R. Max Goepp, M. D. Second edition, thoroughly revised. 1911. 8vo. 715 pages. W. B. Saunders Company, Philadelphia and London.

A Text-book of Surgical Anatomy. By William Francis Campbell, M. D. Second edition, revised with 319 original illustrations. 1911. 8vo. 675 pages. W. B. Saunders Company, Philadelphia and London.

Principles and Practice of Modern Otology. By John F. Barnhill, M. D. and Ernest de Wolfe Wales, B. S., M. D. With 314 original illustrations, many in colors. Second edition, thoroughly revised. 1911. 8vo. W. B. Saunders Company, Philadelphia and London.

Diagnostic and Therapeutic Technic. A Manual of Practical Procedures Employed in Diagnosis and Treatment. By Albert S. Morrow, A. B., M. D. With 815 illustrations, mostly original. 1911. 8vo. 775 pages. W. B. Saunders Company, Philadelphia and London.

A Treatise on Diagnostic Methods of Examination. By Prof. Dr. Hermann Sahli. Edited, with additions, by Nathaniel Bowditch Potter, M. D. Second edition, revised. Authorized translation from the fifth revised and enlarged German edition. 1911. 8vo. 1229 pages. W. B. Saunders Company, Philadelphia and London.

A Hand-book of Practical Treatment. By Many Writers. Edited by John H. Musser, M. D. and A. O. J. Kelly, A. M., M. D. Volume II. 1911. 8vo. 865 pages. W. B. Saunders Company, Philadelphia and London.

Enlargement of the Prostate, its Treatment and Radical Cure. By C. Mansell Moullin, M. D. Oxon., F. R. C. S. Fourth edition. 1911. 8vo. 176 pages. P. Blakiston's Son & Co., Philadelphia.

What Shall I Eat? A Manual of Rational Feeding. By F. X. Gouraud. With a Preface by Prof. Armand Gautier. Only authorized translation into the English language by F. J. Rebman. 1911. 12vo. 379 pages. Rebman Company, New York.

The Anatomic Histological Processes of Bright's Disease and Their Relation to the Functional Changes. Lectures delivered in the Russell Sage Institute of Pathology, City Hospital, New York. During the Winter of 1909. By Horst Oertel. Illustrated. 1910. 8vo. 227 pages. W. B. Saunders Company, Philadelphia and London.

The Experimental Chemotherapy of Spirilloses (Syphilis, Relapsing Fever, Spirillosis of Fowles, Frambœsia). By Paul Ehrlich and S. Hata. With Contributions by H. J. Nichols, J. Iversen, Bitter, and Dreyer. Translated by A. Newbold, and revised by Robert W. Felkin, M. D., F. R. S. E., etc. With 34 tables in the text and 5 plates. 8vo. 181 pages. Rebman Company, New York.

Transactions of the College of Physicians of Philadelphia. Third series. Volume the thirty-second. 1910. 8vo. 442 pages. Printed for the College, Philadelphia.

New and Non-official Remedies, 1911. Containing Descriptions of the Articles which have been Accepted by the Council on Pharmacy and Chemistry of the American Medical Association, Prior to Jan. 1, 1911. 12mo. 282 pages. Press of the American Medical Association, Chicago.

Scientific Memoirs. New Series, No. 39. By Officers of the Medical and Sanitary Departments of the Government of India. *The Applicability to Medico-Legal Practice in India of the Biochemical Tests for the Origin of Blood-stains.* By Lieut.-Colonel W. D. Sutherland, M. B., I. M. S. 1910. Fol. 35 pages. Superintendent Government Printing, Calcutta, India.

Scientific Memoirs. New Series, No. 40. By Officers of the Medical and Sanitary Departments of the Government of India. *The Destruction of Fleas by Exposure to the Sun.* By Captain J. Cunningham, M. D., I. M. S. 1911. 4°. 27 pages. Superintendent of Government Printing, Calcutta, India.

Plaster of Paris and How to Use It. By Martin W. Ware, M. D. Second edition, revised and enlarged. 1911. 12 mo. 99 pages. Surgery Publishing Company, New York.

The Life, History, Function and Inflammation of the Appendix. An Address Delivered to the Clinical Society of Manchester, January, 1911. By Edred M. Corner, M. A., M. C., F. R. C. S. 1911. 8vo. 23 pages. John Bale, Sons & Danielsson, London.

A Text-book of Medicine. By Dr. Adolf V. Strümpell. Fourth American edition translated by permission from the seventeenth revised German edition. With editorial notes, additional chapters, and a section on mental diseases by Herman F. Vickery, A. B., M. D. and Philip Coombs Knapp. With six plates, three of which are in color, and two hundred and twenty-four illustrations in the text. Two volumes. 1911. 8vo. D. Appleton and Company, New York and London.

Chemistry of Food and Nutrition. By Henry C. Sherman, Ph. D. 1911. 12°. 355 pages. The Macmillan Company, New York.

Scientific Memoirs, New Series, No. 41. By Officers of the Medical and Sanitary Departments of the Government of India. *Quinine and its Salts: Their Solubility and Absorbability.* By Captain A. C. MacGilchrist, M. A., M. D., M. R. C. P., I. M. S. 1911. 4to. 46 pages. Superintendent Government Printing, India.

Scientific Memoirs, New Series, No. 42. By Officers of the Medical and Sanitary Departments of the Government of India. Part I. *The Cultivation of the Bacillus of Leprosy and the Treatment of Cases by Means of a Vaccine Prepared from the Cultivations.* By Major E. R. Rost, I. M. S. Part II. *The Cultivation of the Leprosy Bacillus.* By Captain T. S. B. Williams, M. B., I. M. S. 1911. 4to. 23 pages. Superintendent Government Printing, India.

Meningitis, Sinus Thrombosis and Abscess of the Brain. With Appendices on Lumbar Puncture and its Uses, and Diseases of the Nasal Accessory Sinuses. By John Wyllie, M. D. [1910.] 8vo. 258 pages. Paul B. Hoeber, New York.

Disease in Bone and its Detection by the X-rays. By Edward W. H. Shenton, M. R. C. S., Eng., L. R. C. P., Lond. With illustrations. 1911. 8vo. 72 pages. Macmillan and Co., Limited, London.

Central Indiana Hospital for Insane. Report from the Pathological Department. Volume II. 1906-07, 1907-08. Volume III. Fiscal year 1908-1909. 8vo. 1910. Indianapolis.

Transactions of the American Pediatric Society. Edited by Linnaeus Edford La Fétra. Volume XXII. 1910. 8vo. 38 pages. 1911. Reprinted from the Archives of Pediatrics, 1910-1911. E. B. Treat & Co., New York.

The Medical Diseases of Children. By Reginald Miller, M. D. (Lond.), M. R. C. P. 1911. 8vo. 541 pages. John Wright and Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

St. Luke's Hospital. Medical and Surgical Reports. Volume II. 1910. 8vo. 253 pages. Frank B. Howard, Poughkeepsie, N. Y.

A Monograph of the Anopheline Mosquitoes of India. By S. P. James, M. D., D. P. H., I. M. S. and W. Glen Liston, M. D., D. P. H., I. M. S. Second edition, re-written and enlarged. 1911. 4to. 128 pages. Thacker, Spink and Co., Calcutta.

A Practical Medical Dictionary. Of Words Used in Medicine with their Derivation and Pronunciation, Including Dental, Veterinary, Chemical, Botanical, Electrical, Life Insurance and Other Special Terms, etc. By Thomas Lathrop Stedman, A. M., M. D. Illustrated. 1911. 8vo. 1000 pages. William Wood and Company, New York.

Golden Rules of Pediatrics. Aphorisms, Observations, and Precepts on the Science and Art of Pediatrics. Giving Practical Rules for Diagnosis and Prognosis, the Essentials of Infant Feeding, and the Principles of Scientific Treatment. By John Zahorsky, A. B., M. D. With an Introduction by E. W. Saunders, M. D. 1911. 8vo. 284 pages. C. V. Mosby Company, St. Louis.

Contributions to Medical Science. By Howard Taylor Ricketts. 1870-1910. Published as a Tribute to His Memory by His Colleagues under the Auspices of the Chicago Pathological Society. [1911.] 4to. 497 pages. The University of Chicago Press. Chicago, Illinois.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in The Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume II. June, 1911. 8vo. 397 pages. Lea & Febiger, Philadelphia and New York.

The Principles and Practice of Bandaging. By Gwilym G. Davis, M. D. Third edition, revised. Illustrated from original drawings by the author. 1911. 8vo. 128 pages. P. Blakiston's Son & Co., Philadelphia.

American Practice of Surgery. A Complete System of the Science and Art of Surgery. By Representative Surgeons of the United States and Canada. Editors: Joseph D. Bryant, M. D., LL. D.; Albert H. Buck, M. D. Complete in Eight volumes. Profusely illustrated. Volume eight. 1911. 4to. 1146 pages. William Wood and Company, New York.

Diseases of the Skin. By James H. Sequeira, M. D. Lond., F. R. C. P. Lond., F. R. C. S. Eng. With 44 plates in color and 179 other illustrations. 1911. 8vo. 539 pages. P. Blakiston's Son & Co., Philadelphia.

Internal Secretions from a Physiological and Therapeutical Standpoint. By Isaac Ott, A. M., M. D. 1910. 8vo. 133 pages. E. D. Vogel, Easton, Pa.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. The subscription price is $2.00 per year in the United States, Canada, and Mexico; foreign subscriptions $2.50.

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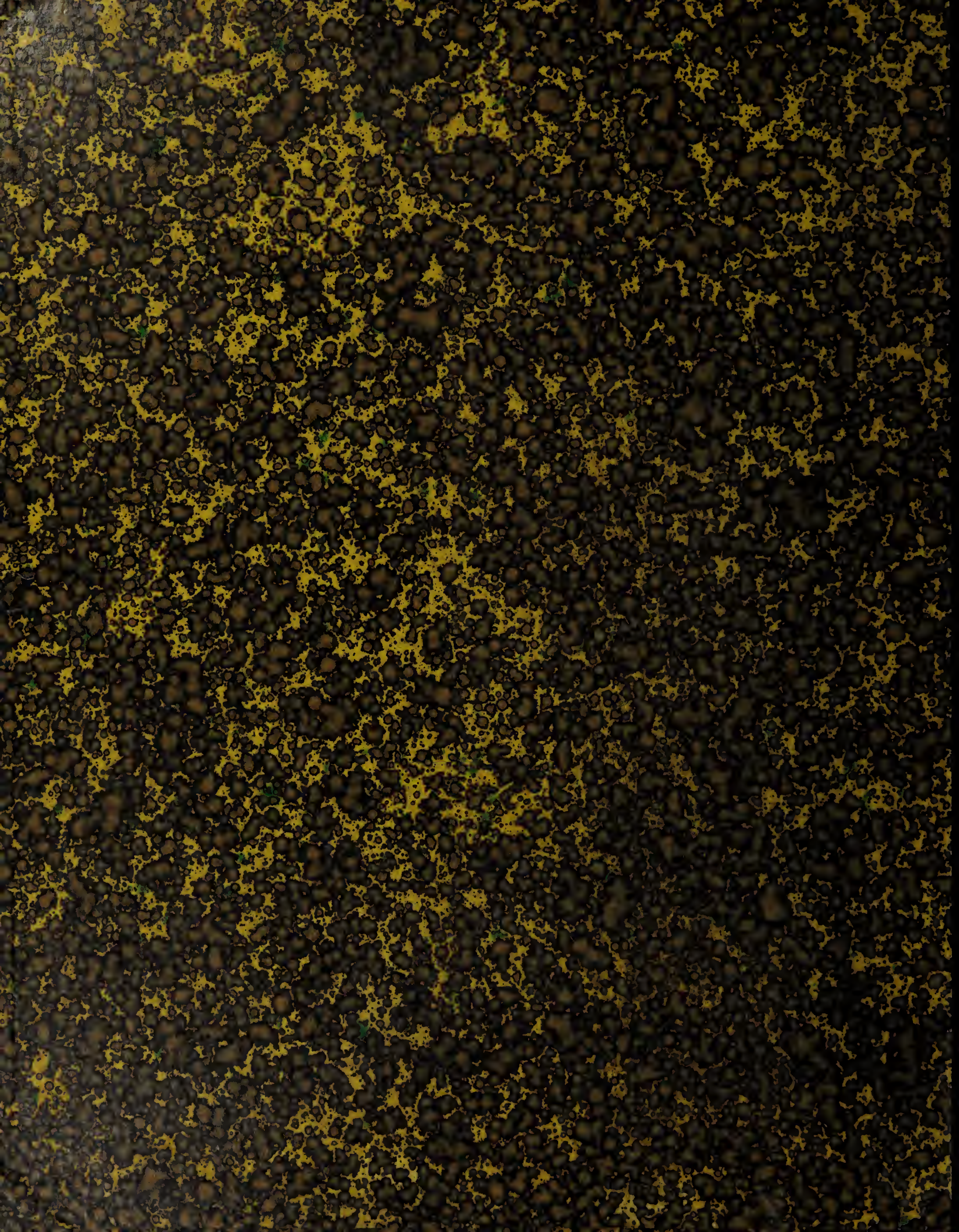

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